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THE THEORY AND APPLICATIONS OF THE EXCHANGE OF INERT GAS AT THE LUNGS AND TISSUES[1]

SEYMOUR S. KETY, M.D.

From the Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania

The respiratory and circulatory systems of the higher animals constitute a single homeostatic complex whose chief function is the maintenance of an optimal molecular concentration of oxygen and carbon dioxide about each cell. This is accomplished by a highly effective combination of physical diffusion and transport together with reversible chemical reactions. The process of diffusion, which alone is sufficient for the metabolic exchange of unicellular organisms, operates in higher animals only across the microscopic spaces between the blood and pulmonary alveoli or peripheral cells. Between the lungs and the body tissues the molecules of gas are transported by the circulating blood in physical solution and, in the case of oxygen and carbon dioxide, in loose chemical combination with certain blood constituents.

The relative magnitudes and time relationships of these various processes are not obvious in the steady state of metabolic exchange. They become apparent, however, when a new molecular species is introduced into the atmosphere which the organism breathes, and, if the new substance happens to be an inert gas, its behavior in the organism may be explained and predicted on the basis of relatively simple physical laws. For the purpose of this discussion an inert gas will be defined as one which dissolves in the blood and tissues in a manner that can be described by Henry's Law, which suffers no change in chemical identity during its passage through the organism, and which is therefore quantitatively recoverable from the organism at any time (54, 105). This definition would include those volatile anesthetic agents which are not chemically altered in the body even though they produce definite physiological effects.

When an inert gas in abruptly introduced at a constant partial pressure into the inspired air, the tissues of the body do not suddenly acquire the gas at this partial pressure. A number of physical processes intervene, each with its own time rate of change, to delay the eventual saturation of the tissues. First, by means of pulmonary ventilation the gas is inspired, diluted with the functional residual air and distributed to the alveolar membrane. Here diffusion occurs and alveolar gas is equilibrated with pulmonary blood which is then distributed via the peripheral arteries to the individual tissues. A second diffusion step now occurs across the capillary membrane, interstitial fluid and cellular membrane and through the intracellular fluid itself. The venous blood from all the tissues returns to the lungs carrying some fraction of its original gas concentration which is thus contributed to the equilibration process occurring at the alveoli. In this manner the alveolar, arterial, tissue and venous tensions of the inert

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gas in question gradually rise toward eventual equilibrium with the tension inspired. Although this sequence of processes is fairly obvious, no single mathematical theory has hitherto been elaborated which embraces them all.

Study of the manner in which inert gases are taken up and released by the body has important implications in many different fields. Perhaps the earliest interest was aroused by the problem of caisson disease (9, 19, 104, 133) in which it soon became apparent that the cause and treatment of the disease lay in the factors governing the saturation and desaturation of body tissues with atmospheric nitrogen during sudden and severe changes in ambient pressure. Similar problems have more recently been encountered in aviation medicine (5). The advent of scientific anesthesiology soon led to a realization of the importance of the solubilities of anesthetic gases and the relationship of physiological factors to the rates of induction and recovery. Since physiological parameters such as alveolar ventilation, functional residual capacity, cardiac output, and blood flow to different tissues determine various phases of inert gas exchange, analysis of certain of those specific phases may be made to yield quantitative information concerning the physiological constants themselves.

THEORY

The Physiological Parameters

At the outset it is necessary to formalize the anatomical and physiological factors involved in inert gas exchange, so that an aggregation of millions of separate processes occurring at microscopic levels in the lung or in a tissue may be represented by a single average process taking place uniformly and simultaneously throughout that system. A certain amount of this type of simplification is essential if there is to be any hope of mathematical treatment of the processes involved. The usefulness and applicability of the theory finally derived, however, depend inversely upon the number of simplifications introduced.

Previous authors, in their mathematical treatments, have employed different symbols for the various factors; in order to avoid confusion it appears worthwhile to adopt some standard system of symbols for the following discussion, and to express the derivations of previous authors in the same system. The author has chosen the following to conform, wherever possible, to the system adopted by the Committee on the Standardization of Symbols used in Respiratory Physiology. The following primary symbols represent certain generic factors: V, a volume; P, a pressure; C, a concentration; M, a volume flow of gas per minute; F, a volume flow of blood per minute; Q, an amount; λ, a partition coefficient; D, a diffusion constant; R, a ratio; S, a surface. These primary symbols are modified by the following subscripts: A, alveolar; E, expired; I, inspired; D, dead space; T, tidal; s, shunt; i, a particular tissue; a, arterial; v, venous; b, blood; p, pulmonary. Specific combinations of these symbols and their physiological definition are discussed in the immediately succeeding paragraphs.

Ventilation

This process, although it is obviously cyclic, has been treated as a continuous function by most of those who have taken it into consideration. The inaccuracy thus introduced is hardly of consequence except where the events occurring in a single breath or in time intervals of a few seconds are being treated. Where interest is confined to the ventilatory process itself it is usually more convenient to represent the process as a series of instantaneous breaths. In this discussion wherever ventilation is taken to be a continuous function, the minute rate of alveolar ventilation (ml. of air washed through the total alveolar volume per minute) will be represented by M_A, the ventilation of the respiratory functional dead space by M_D, and the sum of these by M, the total rate of ventilation (ml./min). In conformity with previous practice inspired air is divided into that fraction remaining unchanged in the physiological dead space and that portion which mixes completely with alveolar gas. Where ventilation is treated as a cyclic process V_T will represent the tidal volume (ml), V_D the physiological dead space (ml) and V_F the effective tidal volume ($V_T - V_D$).

Of considerable importance is that volume of gas (V_A) in the lungs within which each functional tidal volume is ultimately distributed. For the cyclic process this is simply the end inspiratory alveolar gas volume and corresponds to the functional residual capacity[2] (41) plus the effective tidal volume. When ventilation is treated as a continuous process the volume of distribution of inspired gas (V_A) can be shown to correspond closely to the functional residual capacity plus one half the effective tidal volume (*i.e.*, the mid-inspiratory alveolar gas volume).

Blood Flow

The inspired inert gas is not only mixed with alveolar gas but is also distributed into the functional pulmonary blood flow (F_p, ml./min). This represents the portion of the cardiac output which is effectively exposed to alveolar gas. The remaining portion (F_s) represents mixed venous blood shunted past the alveoli through intracardiac communications or unventilated portions of the lung. This normally represents an insignificant fraction of the cardiac output (80) but in certain diseases may assume great importance.

The total left ventricular output (F) is now distributed to the various tissues of the body in a system of parallel circuits, blood flow through a particular tissue being represented by F_i. The liver is a notable exception to the parallel circuit description, as Morales and Smith (91) have pointed out, and represents an organ interposed in series between the abdominal viscera and the heart.

The venous outflow from each tissue, which is assumed to be equal to the arterial inflow, is now mingled with that of all the others and returned to the heart as the mixed venous blood. The concentration of any stable substance in mixed venous blood is therefore the average of its respective concentrations in the venous blood from the several tissues, each weighted by a factor $\left(\frac{F_i}{F}\right)$. Since some tissues are closer to the heart than others, the venous bloods from different tissues are represented in the mixed venous blood at the heart with some degree of time staggering (90). Thus blood from the myocardium may complete its circuit back to the right atrium perhaps twenty or thirty seconds sooner than blood from the toes. Where the time periods under theoretical consideration are of the order of many minutes or hours such a time difference in arrival is probably not important and has usually been neglected. It assumes greater significance, however, when events at the very onset of inert gas uptake are to be examined. The time interval between the outflow of blood from the lungs and the first appearance of that blood in the mixed venous return to the lung is an important and controversial point in some methods for measuring cardiac output.

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[2] Functional residual capacity is defined as the total gas volume in the lungs and respiratory dead space at the end of a normal expiration.

Solubility and Partition Coefficients

Since an inert gas will distribute itself in the various phases (air, blood, tissues), at equilibrium, according to its respective solubility in each, such physical constants constitute important parameters in the exchange process. Solubility of gases in liquids has usually been expressed in two alternative manners. The Bunsen solubility coefficient (α) represents the amount of a particular gas, expressed as ml. reduced to standard temperature and pressure (0°, 760 mm Hg), which is dissolved at complete equilibrium in 1 ml. of a particular liquid when equilibrium has occurred at a specified temperature and a partial pressure for the particular gas of 760 mm Hg. Henry's Law has been shown to apply to the blood solubility of several of the inert gases (50, 61, 109) and probably applies to all (*i.e.*, concentration of gas in liquid is proportional to its partial pressure). The Bunsen coefficient, therefore, yields directly the amount of gas dissolved by 1 ml. of liquid after equilibration at any partial pressure (P) as $\frac{\alpha P}{760}$. The Ostwald solubility coefficient (λ) (sometimes designated α') is similar to the Bunsen coefficient except that the volume of gas dissolved in 1 ml. of liquid is not converted to standard temperature. Thus λ is also the partition coefficient of the gas between the liquid and gas phase after equilibration at any pressure, *i.e.*, λ represents the ratio of the equilibrium concentration of the inert gas in the liquid (expressed in any units) to its concentration in the gas phase (expressed in the same units). It is easily shown that when a quantity of an inert gas Q_x dispersed in another gas is equilibrated with a volume (V_b) of a liquid, the final concentration of x in the liquid will be $\frac{\lambda Q_x}{\lambda V_b + V_a}$ and in the gas phase $\frac{Q_x}{\lambda V_b + V_a}$ where V_a is the final volume of the gas phase and λ the particular partition coefficient. This concept is important in describing inert gas exchange at the lungs. Since both α and λ for a particular gas: liquid system vary with temperature, the particular temperature must be stated; throughout this discussion, unless otherwise noted, values for these coefficients are at 37° C. These two coefficients are related to each other at any temperature (t) as follows:

$$\alpha_t = \lambda_t \left(\frac{273}{t + 273} \right) \tag{1}$$

Another partition coefficient describes the ratio at equilibrium between the concentration of a particular gas in a certain tissue and its concentration in the blood. Throughout this discussion, unless otherwise noted, λ will refer to the blood:gas partition and λ_i to a tissue:blood partition. Values for these coefficients for the different gases have been obtained by numerous investigators and are summarized in Table I. The values for blood:gas partition in general agree well with those for water:gas. This is largely fortuitous and results from the fact that the solubility of most gases is higher in the erythrocyte and lower in plasma (13, 87, 96, 109, 125), the solubility in water lying between the two. For this reason some investigators have found the blood:gas partition to vary with the percentage of red cells in the blood (71, 125). There are comparatively few values for the solubility of gases in tissues probably because of the technical difficulties involved in their determination. Those which are tabulated have been obtained *in vivo* after equilibration of the whole animal or *in vitro* by the use of finely divided tissue. It is interesting to note that except for adipose tissues the tissue:blood partition coefficients are close to unity.

TABLE I

*Values for partition coefficients at 37°–38° C. of some inert gases**

GAS	WATER / GAS	BLOOD / GAS	TISSUE / BLOOD	OIL / WATER
Hydrogen	0.018 (79)			3.1 (79)
Helium	0.0097 (79)	0.0098 (61)		1.7 (79)
Nitrogen	0.0144 (125)	0.0147 (125)	brain 1.1 (24) liver 1.1 (24) fat 5.2 (21)	5.2 (123)
Argon	0.0295 (79)			5.3 (79)
Neon	0.011 (79)			
Krypton	0.051 (79)			9.6 (79)
Xenon	0.097 (79)			20.0 (79)
Radon	0.17 (79)			125 (79)
Ethylene	0.089 (50)	0.140 (50)	brain 1.2 (60) heart 1.0 (60)	14.4 (98)
Nitrous Oxide	0.440 (109)	0.466 (71) 0.473 (97) 0.474 (109)	brain 1.0 (71) heart 1.0 (38)	3.2 (98)
Cyclopropane	0.204 (98)	0.457 (98)		35.0 (98)
Acetylene	0.850 (50)	0.795 (119) 0.842 (50)		
Divinyl ether	1.32 (103)			41.3 (103)
Chloroform	4.6 (89a)	7.3 (89a)	brain 1.0 (94, 122) liver 0.9 (94)	110 (87)
Ethyl ether	15.5 (53)	15.0 (53) 14.9 (107) 14.4 (65)	brain 1.14 (56)	3.2 (98)
Acetone		333 (130)		

* Parenthetical figures are references to the literature.

Diffusion Processes and Diffusion Coefficients

The diffusion process has been assigned roles of varying importance in the exchange of foreign substances, from a practically exclusive one (120) to one of insignificance (64). For an exhaustive discussion of diffusion processes in biological systems the reader is referred to the excellent review by Jacobs (63). Stated in mathematical terms, Fick's law of diffusion in its most general sense is,

$$dQ = -DS \frac{\partial C}{\partial x} dt \tag{2}$$

where dQ represents the amount of a substance diffusing in time dt across a plane of area S under an instantaneous concentration gradient $\frac{\partial C}{\partial x}$ and D is the diffusion coefficient for the substance at a definite temperature in a definite medium; its units are cm^2 per unit of time.

This general equation may be solved to yield useful values for specific geometrical systems or boundary conditions. Since the solution itself depends to a great extent upon the boundary conditions assumed for the system under examination, these particular assumptions become of great importance.

Perhaps the simplest assumption which can be made for the lung or the tissues is to consider diffusion as occurring in parallel streams across a membrane where the concentrations on each side of the membrane, though different and variable with time are uniform at any instant. Such a treatment would apply to the situation in which two aqueous compartments, whose contents were continuously and perfectly stirred, were separated by a watery membrane. In such a situation the diffusion process would take place only within the membrane itself and if the membrane were sufficiently thin (of the order of 10 μ) a steady state of diffusion would almost instantly (Jacobs, p. 63) ensue which would be described by the following particular solution of Fick's equation:

$$\frac{dQ_1}{dt} = -\frac{DS}{H}(C_1 - C_2) \tag{3}$$

that is, the rate of loss of the diffusing substance from the compartment of higher concentration (C_1) would be equal to the specific diffusion coefficient for the substance in the material of the membrane multiplied by the ratio of the area to the thickness (H) of the membrane and multiplied by the concentration difference between the compartments.

This situation is somewhat more complicated where the two compartments may contain different solvents, and the membrane substance itself may constitute still a third phase. Consider first the most complicated system where the two compartments contain different solvents and where the solubility of the gas in question is different in each of the two solvents and in the membrane. Since diffusion occurs only within the membrane the values for concentration in equation 3 refer to the concentration in the membrane and not in the compartments. Now in the face of the membrane exposed to compartment 1 the concentration is $\lambda_1 C_1$ where λ_1 represents the $\frac{\text{membrane}}{\text{solvent 1}}$ partition coefficient for the gas. Similarly the concentration of gas in the face of the membrane exposed to compartment 2 is $\lambda_2 C_2$ where λ_2 is the $\frac{\text{membrane}}{\text{solvent 2}}$ partition coefficient. Equation 3 then becomes,

$$\frac{dQ_1}{dt} = -\frac{DS}{H}(\lambda_1 C_1 - \lambda_2 C_2) \tag{4}$$

In some cases it is more convenient to think in terms of gradients of partial pressure rather than concentration, especially where different phases are involved. Here if P_1 and P_2 be the partial pressure of inert gas on either side of the membrane, then immediately adjacent to compartment 1 the membrane will have a concentration $\frac{\alpha P_1}{760}$ and adjacent to compartment 2 the membrane concentration will be $\frac{\alpha P_2}{760}$, α being the Bunsen solubility coefficient for the gas in the membrane. Equation 3 then becomes,

$$\frac{dQ_1}{dt} = -\frac{DS}{H}\left(\frac{\alpha P_1}{760} - \frac{\alpha P_2}{760}\right) = -\frac{DS\alpha}{H\,760}(P_1 - P_2) \tag{5}$$

Thus from equation 5 the diffusion rate of a gas from the gaseous state through a membrane is directly proportional to its solubility in the membrane. Therefore carbon dioxide, although its diffusion coefficient is lower, diffuses much more rapidly than does oxygen through the pulmonary membrane since its solubility in the membrane solvent (presumably water) is nearly twenty-five times as great.

Values of D in dilute aqueous solutions have been determined for many gases (62); these diffusion coefficients for hydrogen, nitrogen, oxygen and carbon dioxide at temperatures near 20° C are, respectively, 5.2, 2.0, 1.98 and 1.77×10^{-5} cm^2 per second. Krogh (73) found that diffusion coefficients increased approximately by 1% per degree in the region from 0° to 36° C. The coefficients for diffusion through some body tissues have been determined in the case of a few gases (73) (132); they were found to be one third to two thirds their values in water. Recently a beginning has been made in determining coefficients of other gases in living tissues (111); there is need for further work along such lines.

In the treatment of diffusion in the tissues as occurring across a membrane, usually assumed to be that of the capillary, the surface area of this membrane becomes of great importance. This area has been estimated in various tissues from data obtained by several investigators employing injection technics (29, 34, 45, 74, 75, 76, 110, 126). Such studies give quite accurately the number of capillaries open during the injection; the functional surface, however, must be inferred by means of an assumption as to capillary diameters during life. Table II summarizes some of these findings and deductions.

The treatment of diffusion at the tissues as if it occurred only across the capillary membrane into a tissue chamber of spatially uniform concentration has the advantage of simplicity if not verisimilitude. It is perfectly apparent that concentration gradients must exist within the tissue itself during inert gas exchange and it is only by taking them temporarily, at least, into consideration that their importance in the diffusion process may be realized. But in order to take them into consideration one must decide upon some geometrical model of the relationship of capillaries to tissue. One possibility is to consign to each capillary a cylinder of tissue equal in length to that of the capillary and with a volume equal to that of the tissue divided by the number of capillaries (12, 74). On the basis of such a model, governing equations and boundary conditions may be set up (93) and solutions eventually achieved. Such a model might be satisfactory if all the capillaries were disposed in parallel and oriented so that all the arterial ends were on one side. Where the arrangement is more or less random with the arterial end of one cylinder adjacent to the venous end of another there would be gradients not only within but also between the cylinders, introducing almost hopeless complexity into an attempt at mathematical treatment. A relatively simple first approximation may be to consider diffusion as occurring

TABLE II

Capillary density, capillary surface, and maximum diffusion distance in various tissues, from the data of different investigators

TISSUE	SPECIES	REF.	CAPILLARY DENSITY no. per mm^2	CAPILLARY SURFACE cm^2/cm^3	MAXIMUM DIFFUSION DISTANCE μ
Muscle	frog	76	400	190	28
Muscle	horse	76	1400	240	15
Muscle	dog	76	2600	590	11
L. ventricle	human	126	5730	1090	8
R. ventricle	human	126	5680	1080	8
Vent. septum	human	126	4450	850	8
Papillary muscle	human	126	5220	990	8
Heart muscle	mouse	110	5300	1000	8
Cerebral cortex	human	29	1000	190	18
Cerebral cortex	mouse	110	1250	240	16
Cerebellum	mouse	110	1700	330	14
White matter	human	29	300	57	33
Adipose:					
Fat-rich	rat	45	274	52	34
Fat-poor	rat	45	1000	222	18
Liver	mouse	110	4200	800	9
Duodenum	mouse	110	2400	460	11
Pancreas	g. pig	110	1900	360	13
Renal cortex	mouse	110	4500	850	8
Renal medulla	mouse	110	7400	1400	7

radially from the capillary in only two dimensions and to calculate the length of time for the attainment of a specified degree of equilibrium between the average concentration in the tissue and an assumed constant concentration in the capillary (31). Such a treatment is much closer to the truth than the theory of linear diffusion across a membrane since it assumes radial diffusion and includes the tissue in the diffusion process. Copperman (31) has obtained a series of solutions for the general diffusion equation on this basis and in terms of available tissue parameters. This was accomplished by solving the radial diffusion equation,

$$\frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} = \frac{1}{D}\frac{\partial C}{\partial t} \tag{6}$$

with initial conditions: $r = a, C = C_0, a < r \leq R, C = 0$, and with boundary conditions: $r = R, \frac{\delta C}{\delta r} = 0$. For a mean tissue concentration 95% of the final value the exact expression for the time t becomes,

$$\frac{4}{R^2 - a^2} \sum_k \frac{1 - e^{-Dk^2t}}{k^2\left\{\left[\frac{R}{a}\frac{V_0(kR)}{V_0'(ka)}\right]^2 - 1\right\}} = 0.95 \tag{7}$$

where $V_0\,(k\,r) = Y_0\,(k\,a)\,J_0\,(k\,r) - J_0\,(k\,a)\,Y_0\,(k\,r)$ and where k is given by $V_0'\,(k\,R) = 0$. J_0 and Y_0 are the zero order Bessel functions of the first and second kind, respectively. Only the first term in the series is needed for calculation of t. In Table III are presented values for the time in seconds necessary to achieve 95% equilibrium throughout a tissue region of radius R from a capillary of radius $a(= 2.5\ \mu)$ for substances of different diffusion coefficients. Solubility is assumed to be uniform throughout the system. From an examination of the maximum diffusion distances in the various tissues presented in Table II it is apparent that for most tissues and most inert gases, blood:tissue equilibrium, according to this theory, would be nearly complete in about one second.

THE THEORETICAL APPROACH

Since interest was first aroused in this problem there have been only a few mathematical treatments proposed for the description of inert gas behavior in the body. Some of these are highly theoretical, but a large number are frankly empirical, represent merely a formula which best fits the data obtained and have little theoretical justification. The reviewer will attempt to point out in each case the assumptions made, the mathematical results, and their general applicability.

A.) Zuntz (1897), von Schrötter (1906). This theory was apparently first developed by Zuntz (133) and later amplified by von Schrötter (104) to explain the uptake of nitrogen by the body when exposed to an increase in ambient pressure. These authors made the following assumptions. (i) The inspired concentration of nitrogen is immediately transmitted to the alveoli; they therefore neglected the phase of lung washout. In this special case of exposure to increased ambient pressure, such an assumption is perfectly permissible since the alveolar gas is also compressed and increases in nitrogen concentration along with the inspired air. (ii) The alveolar and arterial nitrogen concentrations remain constant following their instantaneous arrival at the new level. In this they neglected the continuous removal of some alveolar nitrogen by the pulmonary blood flow, which, because of the low solubility of nitrogen in blood, introduces little appreciable error. (iii) The circulation was visualized as a somewhat discontinuous function in which the entire blood volume is equilibrated instantaneously in the lung at the new nitrogen tension, then instantaneously equilibrated with all the body tissues simultaneously. The nitrogen-poor venous blood, representing the mean nitrogen tension of the whole body, is now re-equilibrated at the ambient nitrogen tension in the lungs and the process is repeated until the tissues approximate this tension. Thus, if the blood volume, as they assumed, were 1/11th of the nitrogen capacity (tissues + blood) of the body, then in each circulation the tissues would go 1/11th of the way remaining toward complete saturation, and thus describe a logarithmic function. A serious compromise, however, lies in the treatment of the whole body as a single tissue phase equilibrated uniformly with arterial blood so that at all times the nitrogen concentration is uniform throughout all tissues. In reality, as Boycott, Damant and Haldane (19) have pointed out, each tissue has access only to a particular quota of arterial blood and increases in nitrogen concentration at a rate which may be quite at variance with that of another tissue with a different blood flow. This fact does not alter the exponential form of the solution which still remains as the fundamental basis of modern theories; it is necessary, however, to increase the number of terms to embrace these differences among tissues. (iv) No difference in the solubility of nitrogen in blood or in tissues was assumed; this can readily be adjusted by the inclusion of an appropriate partition coefficient. (v) The assumption that complete equilibrium is reached almost instantaneously between a tissue and its blood so that the tension of nitrogen in the tissue is equal to that in its venous blood implies that diffusion is not a limiting factor in this process and also that all the blood flow through a tissue partakes in the equilibration (that is, that there are no arteriovenous shunts). Although the latter assumption

TABLE III

Approximate time in seconds for 95% equilibrium between tissue region of radius R and capillary of radius 2.5 μ for a substance of diffusion coefficient through the tissue of D

$D \times 10^5$	$R = 15\ \mu$	$R = 30\ \mu$	$R = 50\ \mu$
1.0	0.4	2.3	8.3
1.5	0.2	1.5	5.5
2.0	0.2	1.2	4.2
2.5	0.1	0.9	3.8
3.0	0.1	0.7	2.8

may be justified by considering only effective blood flow, no evidence was offered to indicate that diffusion at the tissue is indeed a process rapid enough to be considered instantaneous. A similar assumption has been made by subsequent authors (55, 64) and evidence is being accumulated which may eventually justify it (31, 64).

von Schrötter's actual equation is not nearly so useful as the concepts which Zuntz had previously elaborated. On the basis of these fundamental assumptions, plus the Fick principle (40), it is possible to derive a more generally applicable expression for inert gas uptake by a single tissue. For an inert gas the Fick principle may be stated as follows—the amount of inert gas taken up by the tissue per unit of time is equal to the quantity brought to the tissue by the arterial blood minus the quantity carried away in the venous blood, *i.e.*,

$$\frac{dQ_i}{dt} = F_i(C_a - C_v) \tag{8}$$

assuming that arterial inflow = venous outflow = F_i, and defining a tissue to include its contained blood which constitutes only a few per cent of its total volume (V_i).

Also,

$$\frac{dC_i}{dt} = \frac{1}{V_i}\frac{dQ_i}{dt} = \frac{F_i}{V_i}(C_a - C_v) \tag{9}$$

Now from Zuntz' basic assumption that venous blood from a tissue is in equilibrium with the tissue itself with respect to inert gas, then at all times,

$$C_i = \lambda_i C_v \tag{10}$$

λ_i being a specific partition coefficient for the inert gas in question between tissue (including its contained blood) and blood. From equations 9 and 10 is obtained,

$$\frac{dC_i}{dt} = -\frac{F_i}{\lambda_i V_i}(C_i - \lambda_i C_a) \tag{11}$$

which, if C_a, and therefore $\lambda_i C_a$, are constant, has the following solution for the saturation process:

$$C_i = \lambda_i C_a(1 - e^{-kt}) \quad \text{where} \quad k = \frac{F_i}{\lambda_i V_i} \tag{12}$$

and for the desaturation process:

$$C_i = C_{i_0} e^{-kt} \tag{13}$$

where C_{i_0} is the concentration at the onset of desaturation. From equation 10 similar expressions for C_v are obtained:

$$C_v = C_a(1 - e^{-kt}), \quad \text{for saturation} \tag{14}$$

$$C_v = C_{v_0} e^{-kt}, \quad \text{for desaturation} \tag{15}$$

Thus, on the basis of instantaneous diffusion equilibrium between blood and tissue and with a constant arterial concentration of an inert gas, the concentration in a particular tissue will rise toward its equilibrium value as a single exponential function, with a time constant equal to the blood flow through the tissue divided by the relative capacity of that tissue for the inert gas. Since in reality the body consists of n tissues each with an uptake implicit in equation 11:

$$Q_i = V_i C_i = V_i \lambda_i C_a (1 - e^{-k_i t}) \tag{16}$$

the total amount in the body as a whole (Q) for the saturation process is given by:

$$\begin{aligned} Q &= C_a[V_i\lambda_i(1 - e^{-k_i t}) + V_2\lambda_2(1 - e^{-k_2 t}) + \cdots + V_n\lambda_n(1 - e^{-k_n t})] \\ &= Q_{\infty 1}(1 - e^{-k_1 t}) + Q_{\infty 2}(1 - e^{-k_2 t}) + \cdots + Q_{\infty n}(1 - e^{-k_n t}) \end{aligned} \tag{17}$$

(where the $Q_{\infty i}$ are the quantities of the inert gas in each tissue at complete saturation $= C_a V_i \lambda_i$)
and for the desaturation process, by,

$$Q = Q_1^0 e^{-k_1 t} + Q_2^0 e^{-k_2 t} + \cdots + Q_n^0 e^{-k_n t} \tag{18}$$

where the Q_i^0 are the quantities of the inert gas in each tissue at the onset of desaturation. Since the total quantity eliminated (Q_E) from the body up to any time t must equal the difference between the total quantity present at zero time and the total quantity present at time t,

$$\begin{aligned} Q_E = Q_0 - Q_t &= (Q_1^0 + Q_2^0 + \cdots + Q_n^0) - (Q_1^0 e^{-k_1 t} + Q_2^0 e^{-k_2 t} + \cdots + Q_n^0 e^{-k_n t}) \\ &= Q_1^0(1 - e^{-k_1 t}) + Q_2^0(1 - e^{-k_2 t}) + \cdots + Q_n^0(1 - e^{-k_n t}) \end{aligned} \tag{19}$$

B.) Widmark (1919). The Zuntz-von Schrötter assumptions and the above expressions which the reviewer has derived from them are rigorously applicable only to a state in which the alveolar and arterial concentrations of an inert gas are constant throughout the duration of saturation or desaturation, that is, to a gas of infinitesimal solubility in blood introduced abruptly and at its final concentration into the alveolar spaces. Such a treatment is, therefore, of only limited value in the general problem of inert gas exchange. Widmark (130), on the other hand, derived a relatively simple expression for the elimination (and therefore also the uptake) of inert gases by the body, which is applicable only to gases of extremely great solubility in blood. This author concerned himself especially with the elimination of acetone, the blood:air partition coefficient of which he reported as 333. Because of this preponderant solubility in blood, Widmark could reasonably assume in the case of this gas that in one passage through the lungs the blood loses so little acetone that the concentration in arterial blood is practically identical with that in mixed venous blood. He also assumed that the elimination was sufficiently slow so that the tension of acetone in the blood was always equal to that in the tissues. On the basis of these two assumptions, plus the concept that at the lungs the alveolar air was brought into equilibrium with pulmonary blood, he set up the following differential equation for the elimination of acetone at the lungs:

$$\frac{dQ_s}{dt} = -\frac{M_A C_b}{\lambda} = -\frac{M_A Q_s}{\lambda V_s} \tag{20}$$

where M_A represents alveolar ventilation rate; Q_s, the total quantity of acetone in the body; C_b, the blood concentration; and V_s, the acetone space or the volume of distribution of acetone in the body. Equation 20 may be solved to yield:

$$Q_s(t) = Q_{s_0}e^{-kt} \quad \text{or} \quad C_b(t) = C_{b_0}e^{-kt} \tag{21}$$

where $k = \dfrac{M_A}{\lambda V_s}$

Similarly for saturation at a constant inspired concentration C_I:

$$C_b(t) = \lambda C_I(1 - e^{-kt}) \tag{22}$$

Widmark determined blood acetone concentration during the desaturation process in man and animals and demonstrated a single exponential decay for acetone. He also found, however, that even in the case of a soluble gas like ether ($\lambda = 14.9$), the resulting curve could not be described in terms of a single exponential. Thus Widmark's treatment is of very limited usefulness and is valid only for gases of inordinately high solubility in blood.

C.) Haggard (1924). This theory was elaborated to explain the uptake and elimination of ethyl ether by the body (55). It embraces three of the Zuntz-von Schrötter assumptions (i) that there is a single body tissue mass with a uniform blood flow; (ii) that λ_t is unity; for this particular assumption Haggard obtained empirical data (total quantity absorbed, total weight of the animal, and blood concentration of ether) which appeared to substantiate an average λ_t near unity (54), but possible differences among tissues were neglected; (iii) that there is complete equilibrium between blood and tissue and also between blood and alveolar gas.

In addition, Haggard introduced an important new concept into his theory, one which appears to have been neglected by most subsequent authors. Dealing with a highly soluble gas, he realized that its alveolar concentration would not immediately equal the concentration inspired, but would rise slowly toward that asymptote as the body tissues and venous blood became saturated. Zuntz, who confined his attention to nitrogen could neglect that important fact without making his theory wholly inapplicable; but any mathematical treatment designed to explain the behavior of all inert gases must include this important concept of Haggard.

Haggard treated the ventilation as continuous and recognized and corrected for the respiratory dead space. He then proceeded in a manner reminiscent of Zuntz to treat the phenomena in a discontinuous manner. In the first minute of inhalation of ether at a constant inspired concentration (C_I), the arterial concentration of ether is given by,

$$C_a = \frac{M_A C_I \lambda}{\lambda F + M_A} \tag{23}$$

(In this he neglected dilution of C_I by the functional residual air and assumed that all the cardiac output (F) is equilibrated with alveolar gas.) The quantity of ether absorbed in one minute (Q_1') is,

$$Q_{1'} = FC_a = \frac{FM_A C_I \lambda}{\lambda F + M_A} \tag{24}$$

The quantity of ether exhaled in the first minute ($Q_{E_1'}$) is,

$$Q_{E_1'} = M_A C_I - Q_{1'} = \frac{M_A^2 C_I}{\lambda F + M_A} \tag{25}$$

Assuming that there is a time of one circulation, it would be V_b/F minutes; therefore the quantity of ether absorbed in the first circulation (Q_1) is obtained from equation 24:

$$Q_1 = V_b C_a = \frac{V_b M_A C_I \lambda}{\lambda F + M_A} \tag{26}$$

This quantity is now, after the manner of von Schrötter, equilibrated with all the tissues of the body ($V_n + V_b$); therefore the amount remaining in the blood and brought back to the lungs at the end of the first circulation (Q_{v_1}) is,

$$Q_{v_1} = \left(\frac{M_A C_I \lambda V_b}{\lambda F + M_A}\right)\left(\frac{V_b}{V_n + V_b}\right) = \frac{M_A C_I \lambda V_b^2}{(\lambda F + M_A)(V_n + V_b)} \tag{27}$$

Now in the second circulation, the quantity of ether carried away from the lungs (Q_2) equals the quantity inhaled plus the recirculated quantity (Q_{v1}) distributed between the total blood and air and multiplied by the outflow of blood:

$$Q_2 = \left[\frac{M_A C_I V_b}{F} + \frac{M_A C_I \lambda V_b^2}{(\lambda F + M_A)(V_n + V_b)}\right]\frac{\lambda F}{\lambda F + M_A} \tag{28}$$

This concluded Haggard's formal analysis. He then stated that this process repeated indefinitely is one in which the body, in equal intervals of time, goes a constant fraction of the way toward full saturation. This is the form of a single exponential rise so that Haggard's conclusion is the same as von Schrötter's: $Q = Q_\infty(1 - e^{-kt})$.

Haggard's derivation, although fairly adequate for ether, contains an important oversimplification which precludes its general applicability to any inert gas. Equation 28 neglects the quantity of ether remaining in the lungs at the end of the first circulation and therefore treats the lungs as collapsing completely at each expiration. In the case of a gas as soluble in blood as is ether, little indeed remains in the residual air and this neglect of the pulmonary dilution phase of inert gas exchange introduces only a slight error. This error becomes increasingly great, however, as the inert gas in question decreases in solubility. Even on the assumption of a single tissue phase made by both Zuntz and Haggard, rigorous treatment must yield an expression containing at least two exponential terms determined by tissue *and* lung dilution. It is interesting to note that each of these authors obtained a single exponential by neglecting lung dilution for reasons quite different, and, in each specific and quite limited application, almost justifiable.

Haggard's derivation, however, permitted him to draw the following important conclusions regarding the uptake of ether and other inert gases: (i) The shape of the curve of saturation vs. time for the body is independent of C_I. (ii) From equation 24 he demonstrated that rate of uptake is proportional to $\frac{M_A}{\lambda F + M_A}$ if M_A alone changes, and therefore for very soluble gases (λ large) the rate of absorption is practically proportional to ventilation. For relatively insoluble gases, he pointed out, this dependence on ventilation decreases. (iii) From the same equation he concluded that rate of uptake is proportional to $\frac{\lambda F}{\lambda F + M_A}$ if F alone changes, and, therefore for very soluble gases the rate of uptake is relatively independent of F, becoming increasingly dependent as λ decreases.

D.) Teorell (1937). This author developed a mathematical theory to describe the kinetics of distribution of substances injected into the body (120, 121). He was not directly concerned with the distribution of inhaled gases and none of his derivations is directly applicable to this problem. His point of view, however, must be taken into consideration since it stands in direct antithesis to that of Zuntz. Whereas the latter neglected the diffusion process as a limiting factor in blood:tissue exchange, attributing the rate entirely to circulation, Teorell considered diffusion to be the sole determinant in this exchange and did not include circulation in his derivation. His differential equation for transfer from tissue depot to blood has the form,

$$\frac{dQ_i}{dt} = -k'\left(\frac{Q_i}{V_i} - C_b\right) = -\frac{k'}{V_i}Q_i = -kQ_i \qquad (29)$$

with the assumption that C_b can be neglected. k' represents a permeability coefficient including the diffusion constant for the substance as well as membrane surface and thickness, so that the solution : $Q_i = Q_0e^{-kt}$ is independent of blood flow. Teorell offered no empirical justification for excluding this important parameter and it is difficult to reconcile his concept with the observation (67) that removal of Na^{24} from an injection site is quite sensitive to local circulation and with the even more cogent results of Jones (64) who found identical values for k of two gases of widely differing diffusion constants.

E.) Morales and Smith (1944–48). These authors have made the most exhaustive analysis to this date of the theory of inert gas exchange. In a series of papers (90, 91, 92, 93, 112, 113) they have treated practically all aspects of the problem by a fairly complete mathematical analysis. Their basic approach is perhaps best illustrated by their most recent publication (93) which treats the exchange problem at a single homogenous tissue. With few simplifying assumptions they have set up the following differential equations for the quantities of gas (Q_b) in the blood compartment of a tissue and in the tissue volume itself (Q_i):

$$\frac{dQ_b}{dt} = V_b \frac{dC_b}{dt} = F_i(C_a - C_v) - D_i S_i (C_b - C_i/\lambda_i) \tag{30}$$

$$\frac{dQ_i}{dt} = V_i \frac{dC_i}{dt} = D_i S_i (C_b - C_i/\lambda_i) \tag{31}$$

where D_i is a permeability coefficient for the particular gas and the particular membrane and S_i is the area of the diffusion interface. This treats diffusion as occurring across a definite membrane into a tissue space of uniform concentration C_i.

To evaluate C_b, the mean concentration in tissue capillary blood, they have assumed that it is some constant fraction between C_a and C_v, *i.e.*, $C_a - C_b = r(C_a - C_v)$, and substitute appropriately in equation 30 to get,

$$V_b \frac{dC_b}{dt} = \frac{F_i}{r}(C_a - C_b) - D_i S_i (C_b - C_i/\lambda_i) \tag{32}$$

Equations 31 and 32 are simultaneous differential equations in C_b and C_i and may be solved for each. In order to do this conveniently they have assumed a constant arterial concentration. The solution for C_i is especially pertinent:

$$C_i = \frac{Q_i}{V_i} = \lambda_i C_a (1 + A_1 e^{k_1 t} - A_2 e^{k_2 t}) \tag{33}$$

where $A_1 = \dfrac{k_2}{k_1 - k_2}$ $\qquad A_2 = \dfrac{k_1}{k_1 - k_2}$

and k_1 and k_2 =

$$-\frac{1}{2}\left[\frac{F_i}{V_b r} + \frac{D_i S_i}{V_b}\left(1 + \frac{V_b}{\lambda_i V_i}\right)\right] \pm \frac{1}{2}\left\{\left[\frac{F_i}{V_b r} + \frac{D_i S_i}{V_b}\left(1 + \frac{V_b}{\lambda_i V_i}\right)\right]^2 - \frac{4 F_i D_i S_i}{\lambda_i V_b V_i r}\right\}^{1/2} \tag{34}$$

Thus Morales and Smith, by taking into consideration both blood flow and diffusion in a homogenous tissue, have arrived at an expression for inert gas uptake which contains two exponential terms instead of the single exponential of Zuntz-von Schrötter or Teorell. In an effort to determine whether one of their exponential terms is physically negligible they have reviewed some of the data of others, seeking reasonable values for the physiological parameters in particular tissues (93) and concluding that "whereas in certain cases the von Schrötter approximation might be quantitatively justifiable, in others it would be very poor indeed". They have justifiably insisted upon their more rigorous treatment of the blood: tissue exchange, at least until better evidence is obtained for its simplification.

In another paper (91) Morales and Smith have shown that, where the tissues of the body can be assumed to exist as a distinct parallel arrangement each with its own blood supply, the content of inert gas in the body as a whole at any time t during saturation may then be given by the expression,

$$Q = Q_\infty - \sum_{i=1}^{i=n} (A_{i,1} e^{-k_{i,1}t} + A_{i,2} e^{-k_{i,2}t}) \tag{35}$$

where, as is to be expected from equation 33, there are two exponential terms for each tissue and the *A*'s and *k*'s are determined solely by the physiological parameters of that tissue. In the same communication they have derived an expression for inert gas uptake for tissues in series in which the venous blood from one tissue supplies a succeeding tissue with blood. This also leads to a sum of exponentials where the number of exponential terms is twice the number of tissues, where the decay constants are peculiar to the individual tissue, but where the coefficients are determined by the parameters of all the tissues in series:

$$Q = Q_\infty - \sum_{s=1}^{s=n} (A_{s,1} e^{-k_{s,1}t} + A_{s,2} e^{-k_{s,2}t}) \tag{36}$$

This type of arrangement is seen to an important extent only in the portal circulation through the liver.

In the first paper of the series (112), Smith and Morales derived an expression for inert gas uptake for a limb on the assumption that there is in the limb a single blood chamber supplying all the tissues which remove the inert gas in a competitive manner. It is not unexpected, perhaps, that this assumption leads to a solution in the form of a series of exponential terms of one more than the number of tissues, all of the coefficients and decay constants being determined by the parameters of all the tissues:

$$Q = Q_\infty - \sum_{j=0}^{j=n} A_j e^{-k_j t} \tag{37}$$

It is the opinion of this reviewer that this treatment is needlessly cumbersome and no closer to physiological reality than the distinct parallel system, since individual tissues do in general have their own capillary network and any slight admixture of tissues (*e.g.*, fat cells among muscle fibers) may be taken into account reasonably well in mean parameters for the tissue as a whole.

Morales and Smith have also attempted a mathematical analysis of inert gas exchange at the lung (90). Starting with the drastically limiting assumption that at the instant of the first breath the alveolar concentration is suddenly increased to its final constant value, they derived a set of expressions for four stages of the pulmonary exchange process. Stage (a) persists only for as long a time as the blood spends in the lungs and during this time the partial pressure of the inert gas in the blood is rising exponentially toward that in the alveoli. Stage (b) extends from the end of stage (a) to stage (c), the onset of which is marked by the first return of venous blood containing the inert gas to the lung. Stage (d) begins when the region with the longest roundtrip circulation time just begins to contribute to the venous return to the lung and continues through the remainder of the saturation process. Since this treatment neglects the phase of dilution of inspired air with residual air, and all the ventilatory parameters as well, and neglects the depletion of alveolar gas by carriage of inert gas from the lung in the pulmonary venous blood and the consequent rise of alveolar and arterial blood concentrations as a function of mixed venous concentration, it is applicable only to the special case treated by Zuntz of an insoluble inert gas (N_2) forced into the lung by a sudden increase in ambient pressure or to the special case in which the inspired concentration can be made to vary in order to keep the alveolar concentration constant. It is apparent that the limiting assumptions of this treatment are such as to prevent its applicability generally to the pulmonary exchange of many inert gases.

F.) Kety (1949). This reviewer has had occasion to resort to inert gas exchange theory in the past several years in an effort to comprehend the physiological factors involved in the uptake of nitrous oxide by the arterial blood. Several hundred such curves had been obtained over the early periods of saturation for quite a different purpose (66). It was, however, apparent that the arterial curve varied with important physiological parameters and it seemed desirable to obtain an expression which would demonstrate this relationship. Since all the existing theories save Haggard's assumed a constant arterial concentration and Haggard's treatment was incomplete, it was necessary to develop a theory (70) which comprehended inert gas exchange at the lung.

If the inhaled concentration of an inert gas (C_I, mg./ml.) is held constant and alveolar ventilation is treated as a continuous process represented by M_A (ml./min.), then in a short time (dt), $M'\ dt\ C_I$ mg. of gas are delivered to the alveoli and $M'\ dt\ C_A$ mg. are removed from the alveoli by ventilation. By means of the pulmonary blood flow (F_p ml./min.), $F_p\ dt\ C_v$ mg. of inert gas are delivered during the same time to the alveoli in the mixed venous blood and $F_p\ dt\ C_p$ mg. are removed in the pulmonary venous blood (C_v and C_p representing concentrations of inert gas in mg./ml. in mixed venous and pulmonary venous blood, respectively) thus,

$$\frac{dQ_A}{dt} = V_A\frac{dC_A}{dt} = M_A(C_I - C_A) + F_p(C_v - C_p) \tag{38}$$

This equation neglects the quantity of gas which dissolves in the tissue and blood of the alveolus unless one defines V_A to include not only the alveolar air but also the blood and tissue present in the alveolus with an appropriate partition coefficient correction (*i.e.*, $V_A = V_{air} + \lambda V_{tissue + blood}$). Recent work indicates that for CO_2 this "phantom" residual air is equivalent to an average of 0.7 l. of blood (37).

If one assumes diffusion equilibrium between alveolar gas and pulmonary venous blood then $C_p = \lambda C_A$, where λ is an appropriate partition coefficient. If one is not willing to make such an assumption, another relationship can be obtained by employing a derivation similar to that of Bohr (14): Let C_b represent the variable blood concentration of inert gas along a pulmonary capillary of length L, and x a variable distance along the capillary. Further, let s' and v' represent the diffusion surface and the capillary blood volume, both per unit length of capillary, f the average linear velocity of blood in the capillary, and D' the diffusion coefficient per unit area for the gas across the alveolar membrane. Now assume that the concentration in the gas phase (C_A) is uniform from one end of the capillary to the other.

As an element of blood moves in the capillary from x through dx, it takes up a quantity of gas according to the law of diffusion through a membrane:

$$dQ_b = D's'dx(\lambda C_A - C_b)dt \tag{39}$$

which is also equal to the gain in concentration in the blood (dC_b) multiplied by the volume of blood under consideration ($v'dx$). But $dx = fdt$, whence,

$$dC_bv'fdt = - D's'dx(C_b - \lambda C_A)dt$$

and,

$$\frac{dC_b}{dx} = -\frac{D's'}{v'f}(C_b - \lambda C_A) \tag{40}$$

whence

$$(C_b - \lambda C_A)_x = (C_b - \lambda C_A)_0\, e^{-(D's'/v'f)x} \tag{41}$$

At $x = o$, $C_b = C_v$; at $x = L$, $C_b = C_p$, therefore,

$$C_p - \lambda C_A = (C_v - \lambda C_A)e^{-(D's'/v'f)L} = (C_v - \lambda C_A)e^{-(D'S/F)} \tag{42}$$

where $\frac{S}{F}$ is the ratio of diffusion surface to volume flow of blood for the capillary or the lung as a whole. From equation 42 it is readily shown that

$$C_v - C_p = \theta(C_v - \lambda C_A) \tag{43}$$

where $\theta = 1 - e^{-}\frac{D'S}{F}$ and is probably close to 1 under most circumstances.

The value of $(C_v - C_p)$ obtained in equation 43 may now be substituted in equation 38 to yield:

$$\frac{dC_A}{dt} = \frac{M_A}{V_A}C_I - \frac{M_A + F_p\theta\lambda}{V_A}C_A + \frac{F_p\theta}{V_A}C_v \tag{44}$$

For the case of saturation with an inert gas where at $t = o$, $C_A = C_v = o$, the following solution is obtained,

$$C_A = A_1 C_I (1 - e^{-kt}) + A_2 e^{-kt} \int C_v e^{kt}\, dt \qquad (45)$$

where $A_1 = \dfrac{M_A}{M_A + F_p \theta\lambda}$ $\quad A_2 = \dfrac{F_p \theta}{V_A}$ $\quad k = \dfrac{M_A + F_p \theta\lambda}{V_A}$

Equation 45 represents only a partial solution for the alveolar concentration in terms of physiological parameters since the mixed venous concentration (C_v) remains undefined. It is useful, however, in explaining the differences among the uptake curves of different gases (69) and in assigning appropriate weights to the pulmonary parameters, and it has a certain heuristic value in suggesting means for determining some of the constants involved.

In order to define the arterial concentration (C_a) with close adherence to physiological reality, it is necessary to consider the possibility of venous to arterial shunts by-passing the alveoli. If the ratio of effective pulmonary blood flow (F_p) to total cardiac output (F) be designated as R_p then it is apparent that

$$C_a = R_p C_p + (1 - R_p) C_v \qquad (46$$

which, combined with equation 37 yields,

$$C_a = R_p \theta\lambda C_A + (1 - R_p \theta) C_v \qquad (47)$$

When extra alveolar shunts and diffusion limitation become negligible, equation 47 reduces to $C_a = \lambda C_A$ which should be subject to experimental demonstration. It is interesting that in the case of a single inert gas (as opposed to oxygen (80)) the effect of an extra alveolar shunt would be indistinguishable from that of a diffusion barrier, although the two could be differentiated by employing two gases with markedly different diffusion coefficients. In such a case θ would be different but R_p the same for the two.

Since mixed venous concentration (C_v) in equation 45 remains undefined and since it obviously represents the weighted sum of the venous concentrations from all the separate tissues, it is important now to discuss blood:tissue exchange. A special case of this exchange (the clearance of injected sodium ion from a tissue depot) has previously been published (67); a more general derivation, however, is desirable. The Fick principle, applied to a particular tissue (i), yields as before (equation 8) the equation,

$$\frac{dQ_i}{dt} = V_i \frac{dC_i}{dt} = F_i (C_a - C_{v_i})$$

On Zuntz' assumption that diffusion equilibrium is instantaneous, it has been shown that this reduces to a single exponential expression for C_i. It is now proposed to take the diffusion process into consideration in the manner previously employed at the lung. The assumption is now made that there is some mean tissue concentration of inert gas (C_i) which remains constant during the passage of blood from the arterial to the venous end of the capillary. Since the capillary volume represents less than 5% of the volume of most tissues, marked changes in the blood concentration along the capillary would be reflected in only a slight change in mean tissue concentration. In a manner exactly analogous to that used at the lung the following relationship can be shown to exist for $C_a - C_{v_i}$:

$$C_a - C_{v_i} = m_i(C_a - C_i/\lambda_i) \qquad \text{where } m_i = 1 - e^{-(D_i' S_i/F_i)} \tag{48}$$

which substituted into equation (8) yields,

$$\frac{dC_i}{dt} = \frac{m_i F_i}{V_i \lambda_i}(\lambda_i C_a - C_i) \tag{49}$$

which has the following special solutions:
If C_a is constant and positive (saturation process),

$$C_i = \lambda_i C_a(1 - e^{-k_i t}) \tag{50}$$

If C_a is constant and zero (desaturation process),

$$C_i = C_{i_0} e^{-k_i t} \qquad \text{where } k_i = \frac{m_i F_i}{V_i \lambda_i} \tag{51}$$

These solutions are the same as those derived previously (equations 12 and 13) for similar cases from Zuntz' assumptions except that the k_i now includes a diffusion dependent factor (m_i). This result is to be contrasted with the two term exponential of equation 33 obtained by Morales and Smith by means of a more rigorous derivation. The loss of one exponential term resulted from the assumption that changes in mean tissue inert gas concentration, during the time of passage of an element of blood through the tissue, were negligible in comparison with the concentration change occurring in the blood itself. Although less exact than the expression of Morales and Smith, equations 44 or 45 may be more useful if this assumption can be justified for any particular tissue. Experimental data obtained in two tissues at least (muscle and liver) appear to fit the single exponential form (67, 127), and it is suggested that this less rigorous treatment may be adequate. Where the arterial concentration is variable with time, which unfortunately is often the case, the respective solutions for equation 49 are somewhat more complicated:
For saturation,

$$C_i = \frac{m_i F_i}{V_i} e^{-k_i t} \int C_a e^{k_i t}\, dt \tag{52}$$

For desaturation

$$C_i = C_{i_0} e^{-k_i t} + \frac{m_i F_i}{V_i} e^{-k_i t} \int C_a e^{k_i t}\, dt$$

In a manner similar to that employed at the lung it is possible to set up expressions for C_v assuming the presence of some degree of arterial to venous shunting of blood. Let R_i represent the ratio of effective capillary flow through the tissue to the total capillary plus shunt flow and $C_{v'}$, the resultant venous concentration, then clearly,

$$C_{v_i}' = R_i C_{v_i} + (1 - R_i) C_a$$

whence, from equation 48,

$$C_{v_i}' = R_i \frac{m_i}{\lambda_i} C_i + (1 - R_i m_i) C_a \tag{53}$$

which, in the absence of tissue arteriovenous shunts and with instantaneous diffusion ($R_i = 1 = m_i$) resolves to $C_{v_i} = C_i/\lambda_i$.

Now it is apparent that mixed venous blood entering the lung is a weighted average of the venous blood from the several tissues, so that, neglecting the time stagger mentioned previously,

$$C_v = \frac{F_i}{F} C_{v_i}' + \frac{F_2}{F} C_{v_2}' + \cdots + \frac{F_n}{F} C_{v_n}' \tag{54}$$

so that by means of equations 52 and 53 mixed venous blood has been defined in terms of tissue parameters and arterial blood and by equations 45 and 47 arterial blood has been defined in terms of cardiorespiratory parameters and mixed venous blood. If it were possible to eliminate the blood concentration variables common to both expressions it should be possible to arrive at an expression for the complete lung:blood:tissue exchange of an inert gas entirely in terms of physiological parameters. It is possible to do this to a degree of verisimilitude and, unfortunately, of complexity which is dependent only on the number of assumptions made. The simplest solution is achieved by assuming, with Zuntz, that all the body tissues comprise a single homogeneous tissue mass (V_T) regarding blood flow and gas solubility, and further that equilibrium between alveolar gas and arterial blood and between blood and tissue is complete and, finally, that the blood:tissue partition for the inert gas in question is unity. On the basis of these assumptions m_i and λ_i drop out of equation 49, $C_i = C_v$ and $F_i = F = F_p$. The simultaneous differential equations 38 and 49 now give the following solution for the saturation process:

$$C_A = C_I(1 - A_1 e^{-k_1 t} - A_2 e^{-k_2 t}) \tag{55}$$

where,

$$k_1 \quad \text{and} \quad k_2 = \frac{1}{2}\left\{\frac{M_A + \lambda F}{V_A} + \frac{F}{V_T} \pm \left[\left(\frac{M + \lambda F}{V_A} + \frac{F}{V_T}\right)^2 - \frac{4 M_A F}{V_A V_T}\right]^{\frac{1}{2}}\right\}$$

$$A_1 = \frac{M_A/V_A - k_2}{k_1 - k_2} \qquad A_2 = 1 - A_1$$

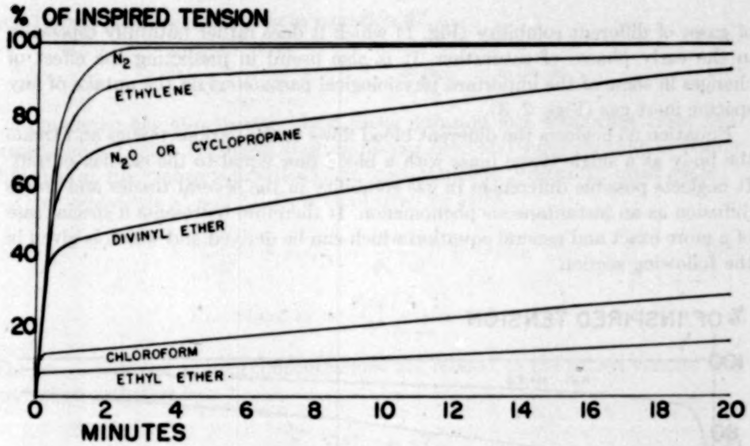

Fig. 1. Alveolar or arterial tensions of several inert gases (expressed as percent of a constant inspired tension) at various times as calculated from equation 55 using values for λ given in Table I. The physiological parameters are assumed to remain constant and to have the following respective values: M_A = 6 l./min., F = 6 l./min., V_A = 3 l., V_T = 70 l.

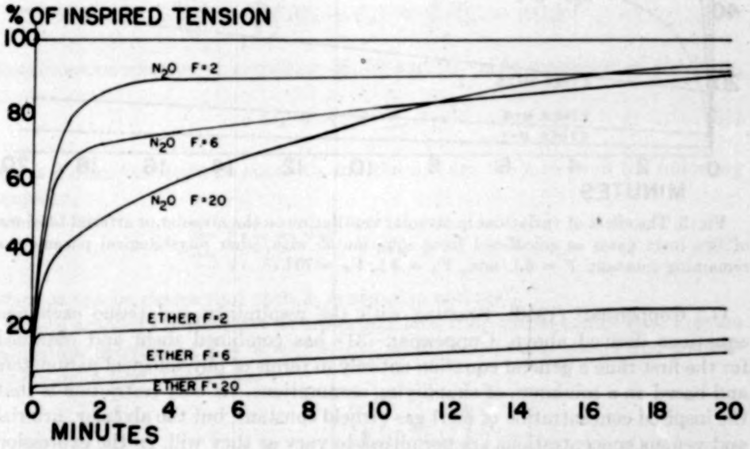

Fig. 2. The effect of variations in cardiac output on the alveolar or arterial tensions of two inert gases as calculated from equation 55 with other physiological parameters remaining constant: M_A = 6 l./min., V_A = 3 l., V_T = 70 l.

Equation 55, although inexact, is nevertheless more complete and general than any previous treatment of this problem. It is applicable to any inert gas regardless of its solubility in blood and in fact can be used to describe the uptake of gases of different solubility (Fig. 1) which it does rather faithfully especially in the early phases of saturation. It is also useful in predicting the effect of changes in some of the important physiological parameters on the uptake of any specific inert gas (Figs. 2, 3).

Equation 55 neglects the different blood flows to the various tissues and treats the body as a single tissue mass with a blood flow equal to the cardiac output. It neglects possible differences in gas solubility in the several tissues and treats diffusion as an instantaneous phenomenon. It therefore represents a special case of a more exact and general equation which can be derived and which is given in the following section.

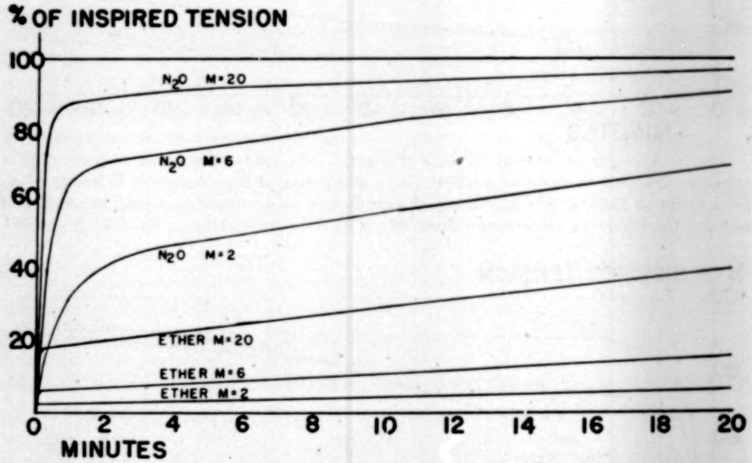

Fig. 3. The effect of variations in alveolar ventilation on the alveolar or arterial tensions of two inert gases as calculated from equation 55 with other physiological parameters remaining constant: $F = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

G.) Copperman (1950). Starting with the respiratory and tissue exchange equations derived above, Copperman (31) has combined them and obtained for the first time a general equation entirely in terms of physiological parameters and based on a minimum of simplifying assumptions. Its only restriction is that the inspired concentration of inert gas be held constant, but the alveolar, arterial and venous concentrations are permitted to vary as they will. In the expression derived here he has chosen to neglect the presence of shunts at the lung and tissues ($R_p = 1 = R_i$) and to assume instantaneous diffusion at the lung ($\theta = 1$) but retaining the diffusion process at the tissues. He obtains therefore from equation 8,

$$\frac{dC_i}{dt} = \frac{F_i}{V_i}(\lambda C_A - C_{v_i}) \tag{56}$$

and from a Bohr derivation as in equation 42,

$$\frac{\lambda_i \lambda C_A - C_i}{\lambda_i C_{vi} - C_i} = e^{D_i' s_i / F_i} = \psi_i \qquad \psi > 1 \tag{57}$$

Copperman has also treated blood-tissue diffusion in a somewhat more rigorous fashion (Table III) than that employed here and suggests that in reality diffusion at the tissues is practically an instantaneous process for most gases.

From equations 56 and 57, C_i is eliminated to yield,

$$\frac{dC_{v_i}}{dt} + r_i C_{v_i} = \frac{\lambda}{\psi_i} \frac{dC_A}{dt} + \lambda r_i C_A \tag{58}$$

$$\text{where } r_i = \frac{F_i(\psi_i - 1)}{V_i \lambda_i \psi_i} > 0$$

The $(n - 1)$ tissue venous concentrations are related to the mixed venous concentration as before by,

$$\sum_{i=1}^{n-1} F_i C_{v_i} = F C_v \tag{59}$$

Finally C_v and C_A are related by the equation for respiratory exchange (equation 38):

$$\frac{dC_A}{dt} = \frac{M_A}{V_A}(C_I - C_A) + \frac{F}{V_A}(C_v - \lambda C_A) \tag{60}$$

Simultaneous solution of equations 58, 59 and 60 yields a solution of the form,

$$C_A = A_0 + \sum_{j=1}^{n} A_j e^{k_j t} \tag{61}$$

where A_0 can be shown to equal C_I and the k_j's are the n roots of the following equation,

$$\lambda \sum_{i=1}^{n-1} \frac{F_i}{\psi_i} \frac{k_j + \psi_i r_i}{k_j + r_i} = M_A + \lambda F + V_A k_j \tag{62}$$

where it can be shown that each k_j is negative and real.

The n arbitrary coefficients A_j are determined from initial conditions: For the saturation process, at $t = o$, $C_A = C_{v_1} = C_{v_2} = \cdots C_{v_{n-1}} = 0$ and the following definition is achieved,

$$A_j = -\frac{\prod_{i=1}^{n-1}\left(1 + \frac{k_j}{r_i}\right)}{\prod_{\substack{i=1 \\ i \neq j}}^{n}\left(1 - \frac{k_j}{k_i}\right)} C_I \tag{63}$$

The A$_j$'s are shown to be real and, in every particular case examined, to be negative, although a rigorous proof that they are always negative has not been obtained. The alveolar concentration of an inert gas inhaled at a constant concentration has therefore the form:

$$C_A = C_I(1 - A_1e^{-k_1t} - A_2e^{-k_2t} - \cdots - A_ne^{-k_nt}) \tag{64}$$

where the coefficients A_1 to A_n and the decay constants k_1 to k_n are related in an obvious manner to corresponding coefficients and decay constants defined by equations 62 and 63 entirely in terms of physiological parameters. It is immediately apparent that these A's and k's are not specifically referable each to a particular tissue, but that all are determined by all the parameters. It may be possible by appropriate assumptions to simplify these expressions so that each coefficient and decay constant refers to a particular tissue. It will always be necessary, however, to justify such assumptions by experimental proof.

THE EMPIRICAL APPROACH

A wealth of experimental data pertinent to the problem of inert gas exchange has been accumulated since the earliest interest in the role of nitrogen in decompression sickness. In reporting their results most investigators made use of some mathematical expression which they or others had previously derived or which they found by trial from their data. With one notable exception (117) these expressions have assumed the exponential form, as indeed, have all the theoretically derived equations.

Inert Gas Exchange in the Body as a Whole

Campbell and Hill (21) in 1931 reported measurements on the elimination of nitrogen by the lungs effected by the breathing of practically pure oxygen. They distinguished between the nitrogen present in the residual air at the beginning of oxygen inhalation and that subsequently eliminated from the body tissues via the pulmonary circulation by means of an initial flushing of the lung during one minute of hyperventilation, and measured the residual volume of the lung in this manner. Although they did not attempt a mathematical analysis of the nitrogen elimination process they report that its rate decreased with time and suggested that the slower rates represented regions with poor blood supply and therefore slower diffusion. They also observed that after exposure to several atmospheres of nitrogen the quantity of that gas eliminated in the denitrogenation process was proportional to original saturation pressure, *i.e.*, the conditions of Henry's law were satisfied for the uptake of nitrogen by the body.

In the United States much of the early and fundamental work on the exchange of nitrogen and other inert gases was done by Behnke and his associates (4, 6, 7, 108). By means of considerably improved technics they studied the elimination of nitrogen during oxygen breathing of several hours duration (6). Total nitrogen elimination beginning after an initial 5-minute period for lung washout was found to fit the expression,

$$Q_B = A_1(1 - e^{-k_1t}) + A_2(1 - e^{-k_2t}).$$

The following values for the constants were obtained in one experiment: A_1 = 458 ml., k_1 = 0.098 min.$^{-1}$, A_2 = 382 ml., k_2 = 0.0085 min.$^{-1}$. These investigators have refrained from suggesting an interpretation of the k's in terms of physiological parameters. Their original interpretation of the A's as representing the quantities of nitrogen initially in the water and fat components of the body, although supported by the reasonable values thus obtained for these components, was a rough approximation. More recent analysis of Behnke's nitrogen elimination data by Smith and Morales (4) has yielded a three term exponential expression:

$$Q_N = 172(1 - e^{-0.13t}) + 353(1 - e^{-0.028t}) + 255(1 - e^{-0.0079t})$$

Underwood and Diaz (124) have reported an interesting series of experiments in which a solution of radon was injected intravenously in dogs and the quantity exhaled over the next several minutes measured by means of a Geiger counter. The elimination was found to fit an exponential decay curve ($k = 0.66 \text{ min}^{-1}$). They suggest that the elimination curve is actually a series of exponentially decaying functions, without attempting what might have been a fairly taxing theoretical analysis.

A unique expression for the quantity of nitrogen eliminated during breathing of oxygen has been obtained by Stevens and his collaborators (117). In 85 carefully performed experiments on 37 individuals they found that after an initial period of lung washout, the total nitrogen eliminated (Q_N) in time t from 1 to 20 minutes and in some cases up to several hours could be expressed as $Q_N = a\,t^b$, a and b being arbitrary constants. Although this frankly empirical expression enables one to report cumbersome nitrogen elimination data in terms of only two numbers, that is probably its greatest value, since there does not appear to be a theoretical basis for the expression used in terms of physiological mechanisms.

Jones has recently summarized the results of extensive experiments performed over the past several years (64); these have included studies with many different gases and of the uptake and elimination by the body as a whole as well as that confined to local regions. In his studies of inert gas exchange for the body as a whole, Jones has assumed expressions for the total quantity exhaled or absorbed up to time t, or in differential form, the time rate of these processes at any instant:

$$Q_N = A_1(1 - e^{-k_1t}) + A_2(1 - e^{-k_2t}) + \cdots + A_n(1 - e^{-k_nt})$$
$$dQ_N/dt = k_1A_1e^{-k_1t} + k_2A_2e^{-k_2t} + \cdots + k_nA_ne^{-k_nt}$$

His data fit such expressions to a satisfactory degree. For example, one of the best resolved curves yielded for nitrogen (exclusive of initial lung nitrogen) the following values in units of ml. for the A's and min.$^{-1}$ for the k's: $A_1 = 111$, $k_1 = 0.462$; $A_2 = 193$; $k_2 = 0.087$; $A_3 = 428$, $k_3 = 0.024$; $A_4 = 95$, $k_4 = 0.008$; $A_5 = 600$, $k_5 = 0.0025$.

Jones was able to derive physiological quantities from these empirical constants by assuming first, that each pair of constants is representative of a single tissue or group of tissues having similar perfusion characteristics, and second, that the constants themselves are related quite simply to these physiological parameters. A_i was then taken to denote the total quantity of the inert gas in question in a particular tissue or group of tissues after full saturation at the partial pressure in question, that is $A_i = C_I\lambda\lambda_iV_i$ where C_I is the concentration in inspired air during the saturation process. Similarly k_i was considered to represent the perfusion rate of the tissue in terms of blood flow and tissue capacity for the inert gas, $k_i = F_i/V_i\lambda_i$. Although he presented no theoretical justification for these simplifications, Jones offered in evidence (i) the fact that among the gases nitrogen, krypton, helium, and xenon no appreciable differences were found in the respective k's obtained and (ii) that the total amounts of inert gas exchanging could be predicted from their solubility in body tissues. Such data are quite pertinent and the number of such experiments could with profit be extended. However, direct and conclusive proof is still to be obtained that the empirical constants (k) of Jones are in fact simply tissue perfusion rates.

The equations 62 and 63 of Copperman indicate that none of the A's and k's of an expression like that of Jones is in general defined exclusively by the parameters of a single tissue or group of tissues. It is probable, however, that Jones, by a combination of relatively insoluble gases and an initial period of hyperventilation, succeeded in achieving arterial concentrations of the inert gases which were practically constant over most of the experimental period. Under such special circumstances the general equation could be approximated by one in which each of the j terms could be referred to a single tissue or group of tissues. It is important to point out, however, that such an approximation is not generally permissible and would not be valid in the case of more soluble gases, *e.g.*, the anesthetic gases.

Inert Gas Exchange in the Individual Tissues or Organs

Early studies on this phenomenon as it occurs within the living body were few in number and confined to experiments in animals which could be sacrificed at intervals during the gas exchange process and the tissues in question analyzed for their content of the inert gas (24). The difficulties of handling and analyzing tissues without loss of these volatile constituents are obvious, and results must often be interpreted with caution.

The recent availability of radioactive isotopes of the elements has made possible a means for studying exchange phenomena in living tissues with a minimum of disturbance to the phenomena themselves. By means of suitably placed and properly shielded detecting instruments, the time course of the uptake or removal of a radioactive substance in particular parts of the body may be obtained if the emanations are sufficiently penetrating (64, 67, 113, 123, 127). Such technics, although admirably suited to the problems of local inert gas exchange, are not entirely free from objections. The problem of shielding the detecting device from radiation arising elsewhere than the region of interest is often a difficult one, and safety requirements place a definite limit on the dosages permissible in man. In addition, conversion from radiation intensity in the detecting instrument to concentrations or quantities in the tissues involve complicated calculations, assumptions, or the preparation of satisfactory models. Most investigators have not attempted to calculate absolute quantities involved, since, fortunately, the time constant of an exponential function is independent of the units in which the function is measured.

Inert gas exchange in the *brain* has been studied by both technics (24, 64, 71). Campbell and Hill (24) reported a very slow rate for the uptake of nitrogen by the brains of goats exposed to 4, 5, and 6 atmospheres of pressure, observing only 50% saturation in that organ at the end of an exposure lasting 3 to 5 hours (24). Kety, Harmel, Broomell and Rhode (71), employing a similar but perhaps more precise technic, obtained data indicating, on the contrary, practically complete equilibrium with the inspired tension of nitrous oxide within ten minutes. They were also able to demonstrate a very rapid loss of this gas from the exposed brain unless certain precautions were taken and thus probably to explain the low nitrogen contents found by Campbell and Hill. By means of radioactive krypton, Jones (64) has demonstrated a very rapid uptake of this gas by the human brain which yields two time constants of 1.4 and 0.35 min.$^{-1}$, respectively. On that basis one would expect a saturation of better than 98% at the end of 10 minutes, a prediction in good agreement with the results above obtained for nitrous oxide in dogs. This reviewer has made mathematical analyses of arterial and cerebral venous curves of nitrous oxide which confirm Jones' finding of a system of two components, possibly gray and white matter.

Campbell and Hill (24) also obtained results which suggest a slow uptake of nitrogen by the *livers* of goats exposed to increased ambient pressures. Their results are not in accord with expectation on the basis of the known rapid blood flow through the human liver (20) and the rapid clearance rate (0.4 min.$^{-1}$) of radioactive sodium from this organ obtained by Wechsler and associates (127).

The radioactive isotope of krypton (Kr^{79,81}) has been used to study the dynamics of inert gas exchange in the *extremities* of man (64, 113, 123) and animals (30). In studies on the normal human hand, Tobias and coworkers (123) found a three component uptake curve with average *k*'s of 0.16, 0.021 and 0.0037 min.$^{-1}$ in a series of 9 cases. In one case Morales and Smith (92) obtained *k*'s of 0.11, 0.058 and 0.02 min.$^{-1}$ for the hand. They calculated theoretical magnitudes for these constants on the basis of known and assumed reasonable values for the physiological parameters and obtained 0.17, 0.03 and 0.003 min.$^{-1}$. Although these theoretical constants agree only within an order of magnitude with the empirical values found by Morales and Smith it is interesting to note that they are in almost perfect agreement with the values found by Tobias. In a series of 7 studies at the popliteal region Tobias found two components with *k*'s of 0.013 and 0.0018 min.$^{-1}$, respectively.

Three important tissues are included in these studies upon the extremities of man: muscle, fat and skin, not to mention bone and bone marrow. Some authors have attempted to relate the *k*'s to these tissue components; in general, however, there are practically no studies on the uptake or removal of inert gases by pure tissues. Whitely and McElroy (128, 129) have reported denitrogenation curves on samples of blood draining *muscle* or *fat*. Although they have not attempted mathematical analyses of their curves there appear to be two exponential components in each, one of which is extremely slow. It is difficult to exclude the possibility of a continuous diffusion of nitrogen from the surrounding air into the tissues as an explanation of this slow component, since apparently little precaution was taken to exclude it, and since others (4) have demonstrated that this phenomenon may occur in the presence of open wounds. Kety (67) has demonstrated an average clearance rate of 0.05 min.^{-1} for Na^{24} ion injected into the human gastrocnemius muscle, but the relationship between this and the exchange rate of an inert gas has not yet been investigated.

The rate of inert gas exchange through the intact human *skin* was investigated by Behnke and Willmon (8) by means of an ingenious technic. They found, at room temperature and under a gradient of close to one atmosphere, that some 50 ml. of helium were able to diffuse through practically the entire cutaneous surface per hour. Nitrogen diffused through the skin approximately one half as rapidly as helium under similar circumstances. The cutaneous diffusion of these gases was quite sensitive to temperatures above 29° C. and increased rapidly so that at a temperature of 35° C. the total diffusion of helium was 160 ml./hr. By means of their data and the Fick principle these authors calculated a total cutaneous blood flow of 333 ml./min. at 35° C. This is probably an underestimate of the true value since they assumed complete diffusion equilibrium between the ambient helium tension and that in cutaneous venous blood, which is not likely to have occurred through the fairly gross distances involved. Several other gases have also been shown to diffuse through the intact skin (99).

Campbell and Hill (22) studied the uptake of nitrogen by the *bone marrow* and found it to be quite slow (25% of full saturation in one hour). Jones (64) has compared these results with his own obtained by a different method.

The uptake of radioactive krypton from the *stomach* and *intestinal tract* was qualitatively demonstrated by Tobias and his associates (123). This was found to occur fairly rapidly when the gas was introduced into the duodenum, but at a much slower rate from the stomach or colon.

Ferris, Molle and Ryder (39) have recorded several interesting examples of the time course of nitrogen concentration in blood from various sites in man during denitrogenation. These include analyses of arterial, internal jugular and antecubital venous blood and ascitic, cerebrospinal and synovial fluid. The nitrogen concentration in arterial and internal jugular venous blood fell rapidly while the clearance from cerebrospinal fluid was quite slow.

The accumulation and removal of some anesthetic gases from artificial subcutaneous and peritoneal pockets have been examined by one group (105). Cyclopropane was found to appear in and disappear from these pockets at a rate approximately twice that of ethylene. Since the ratio of exposed surface to volume in this situation is extremely small, this would be expected to be a diffusion limited process and as such the respective solubilities of the two gases in water should be the determining factor in the rate of exchange (equation 5). The results found are entirely in accord with the fact that this solubility for cyclopropane is twice that for ethylene (Table I).

The Effects of Changes in the Physiological Parameters on Inert Gas Exchange

Haggard (58) has reported the results of experiments designed to test the effects of varying certain cardiorespiratory factors on the uptake and elimination of ethyl ether by the body. He showed that pulmonary ventilation was a factor of prime importance in the case of this very soluble gas. Underwood and Diaz (124) also showed that hyperventilation increases considerably the rate of elimination of radon, another soluble gas, while Stevens (117) demonstrated that the elimination of relatively insoluble nitrogen from the body, excluding the initial quantity present in the alveoli (43), was little affected by prolonged hyperventilation. All these findings are compatible with equation 45, the general expression for gas exchange at the lungs.

Exercise has been shown by Behnke and Willmon (7) to increase the rate of nitrogen elimination via the lungs, but largely during the first thirty minutes of the denitrogenation curve. This may probably be explained on the basis that nitrogen, being slightly soluble in blood, achieves a constant and low arterial concentration fairly early so that the subsequent elimination is a function largely of tissue parameters. Furthermore, muscular exercise probably does not increase the exchange processes in adipose tissue which constitute the bulk of the slower components and thus the latter part of the denitrogenation process is not accelerated. Locally, muscular exercise has been shown to increase the rate of gas exchange in the limbs (30) and the clearance of nitrogen (128) or Na^{24} (67) from the active muscles.

The local rate of exchange of inert gas or of sodium can be increased by warming the region (30, 39), by reactive hypermia (67), or by vasodilating drugs (30). Cooling the extremity or the administration of vasoconstrictors (30) has been shown to decrease these rates of exchange. These results may be explained by changes in effective blood flow through the tissue or by changes in the number of functioning capillaries with consequent effects on capillary surface and mean diffusion distance. It is quite difficult to differentiate among those effects which probably occur simultaneously and affect the exchange rate in the same direction.

There remains a wide gap at the present time between the theory of inert gas exchange at the lungs and tissues and empirical data with which to substantiate the numerous assumptions or to test the predictions of theory. Although it is apparent that the exchange processes are everywhere dependent on physiological and physical parameters, much remains to be done in relating those factors rigorously to the phenomena which may be observed in the expired air, the arterial or venous blood, or directly in the various tissues.

THE APPLICATIONS OF INERT GAS EXCHANGE TO MEDICAL PROBLEMS

The earliest interest in this general problem was stimulated by the astute demonstration of the remarkable physiologist, Paul Bert (9), that decompression illness was probably due to the release of dissolved gases from the tissues. The mass of theory and data which has been acquired since that time and which has amply substantiated that observation is well summarized in a number of recent excellent reviews (5, 25, 64).

The practical implications of these phenomena, however, have not been confined to decompression sickness. Their obvious dependence on physiological factors soon led to numerous attempts to measure these factors by study of various aspects of inert gas exchange as a result of which a number of clinically useful methods have been developed for measurement of pulmonary ventilation, cardiac output, and blood flow through various organs.

A.) *Pulmonary Ventilation*

Examination of the general pulmonary exchange equation developed earlier (equation 45) reveals that for the special case of gases with very low solubility in blood the term containing C_v becomes negligible and

$$C_A = C_I(1 - e^{-(M_A/V_A)t}) \qquad \begin{matrix} \lambda << 1 \\ C_v << C_A \end{matrix} \tag{65}$$

In other words under such circumstances the lungs are acting like bellows, continuously diluting the inspired gas with the mid-inspiratory lung volume. This equation may readily be converted to one which treats ventilation as a discontinuous process (1a, 36, 44). After *n* breaths of nitrogen-free oxygen, the concentrations of nitrogen in alveolar and expired air would be as follows:

$$C_{A_n} = C_0\left(\frac{V_R}{V_R + V_T}\right)^n \tag{66}$$

$$C_{E_n} = \left(\frac{V_T}{V_T + V_D}\right) C_0\left(\frac{V_R}{V_R + V_T}\right)^n \tag{67}$$

where $C_I = O$, C_0 = initial nitrogen concentration, V_T, V_D, V_R are, respectively, effective tidal, physiological dead space, and functional residual volumes.

Darling, Cournand and Richards (36) include a correction for the small contribution of nitrogen to the alveolar gas from the mixed venous blood. This rate of nitrogen elimination is assumed to remain constant; it was determined empirically and found to vary with surface area of the body, averaging about 200 ml. in seven minutes for a normal adult (33, 35). Measurement of lung volume has been accomplished with the use of hydrogen (11, 88), nitrogen (15, 21, 28, 33, 35, 36, 44, 81) or helium (46, 89, 131) in one or several breaths.

It was soon realized that some unevenness existed even in normal pulmonary ventilation (11, 42) and that this became quite marked in patients with emphysema. Individual measurement of these ventilatory components from analysis of expired air has been accomplished independently by Robertson, Siri and Jones (101a) and by Fowler (44).

B.) *Cardiac Output*

Bornstein (16) was apparently the first to apply the principles of inert gas exchange to measurement of pulmonary blood flow. Starting with Zuntz' concept of gas exchange (133), he reasoned that the quantity of nitrogen eliminated in unit time during oxygen breathing should be proportional to the tissue—alveolar nitrogen gradient and to the pulmonary blood flow or cardiac output. He devised a technic for measuring the nitrogen eliminated and the mean alveolar nitrogen tension by oxygen rebreathing from a rubber bag and calculating relative values for cardiac output in the same individual under different conditions compared to the resting state.

Krogh and Lindhard (77) soon pointed out that if Bornstein's determination were to be done within a time short enough to prevent the recirculation of blood through the lungs, it would then be possible to obtain an absolute value for pulmonary blood flow. They devised a technic for making measurements within a period of about 15 seconds and in this way hoped to avoid recirculation. Their method employed 10–25% nitrous oxide as the inert gas and consisted essentially in measuring the loss of this gas from the alveoli during an accurately determined period of breath-holding following its introduction into the alveoli by means of one or several deep breaths. By simultaneous measurement of oxygen loss from the alveolar gas they found an increase in oxygen consumption during the determination which they attributed to an increased pulmonary blood flow induced by the procedure itself. On the assumption that only pulmonary blood flow and not the mixed venous oxygen content was altered by the short procedure, they reduced the experimentally determined values for pulmonary blood flow to corrected values by the use of a factor which was the ratio of the experimental to the pre-experimental oxygen consumption. The latter was determined in the usual manner immediately before the nitrous oxide inhalation. Most of the resting values for pulmonary blood flow thus obtained were within 4 to 5 l./min. and showed approximately a four-fold increase during exercise. Krogh and Lindhard's method was followed by a great surge of methods and modifications, all of which utilized the principle of inert gas exchange (17, 18, 27, 78, 76, 82, 83, 84, 85, 86, 114, 116).

After an elaborate evaluation and modification of Bornstein's method (86), Marshall and Grollman developed a technic using ethylene (85), which Grollman subsequently modified by substituting acetylene (49, 51). This method is essentially that of Krogh and Lindhard except that the technic for determining the quantity of inert gas absorbed was improved by introducing a procedure of rapid rebreathing from a rubber bag. Thus the alveolar gas and the gas in the bag were in essential equilibrium throughout the procedure, permitting the calculation of gas removed from the alveolar-bag system to be made from samples taken at 15 seconds and 8 seconds later. The acetylene technic also incorporates the ingenious oxygen correction which Krogh and Lindhard introduced for minimizing the effect of the procedure *per se* on pulmonary blood flow. In 50 young adults, Grollman (51) obtained mean values of 3.87 l./min. for cardiac output (pulmonary blood flow) and 2.21 l./min./m.^{2} for cardiac index.

All the technics above are subject to certain errors and difficulties. The errors associated with analytical methods, correction for change in gas volume during absorption, etc. simply require their recognition and sufficient patience for satisfactory solution. The problem of obtaining representative samples of alveolar air is a real one although it is likely that by the technic of Marshall and Grollman satisfactory uniformity could be achieved in normal subjects. In patients with pulmonary disease and uneven ventilation even this method might be open to some question. The problems of the uptake of the inert gas by the lung tissue itself and by its contained blood volume (as distinct from its blood flow) and the possibility of loss by diffusion into the other thoracic structures were all considered by Krogh and Lindhard but often overlooked by subsequent investigators. Even the former pair of workers, however, achieved only a partial solution to the problem by a short preliminary period of equilibration.

An important difficulty in these methods and the one which has been largely responsible for their disrepute up to the present time has been the fact that venous blood carrying some of the inert gas in question returns to the lungs before a single determination has been completed. Although most of the proponents of these methods have insisted that significant recirculation does not occur during their determination others have emphasized the extreme rapidity with which some venous blood returns to the heart. In the dog (59, 115) significant recirculation has been shown to occur in 15 seconds. Baumann and Grollman (2), by direct cardiac puncture in man, found the mixed venous blood concentration of acetylene to be almost 6% of the arterial in samples taken from 12 to 20 seconds after the first inhalation of that gas. In 25 to 30 seconds this had reached 12% and in 33 to 37 seconds, 18% of the arterial level. By less direct procedures Gladstone (47) and Adams and Sandiford (1) have found evidence for recirculation of blood containing acetylene in 10 and 20 seconds, respectively, and quite recently mixed venous blood samples obtained by cardiac catheterization (26) indicated that recirculation begins at about 8 seconds. These investigators (26), in an excellent critical evaluation of the Grollman method, have discovered a number of factors which together explain the discrepancy between that method and the direct Fick determination. They suggest several corrections which may permit the indirect method to yield valid results. Methods have been described recently (1, 48) in which more serious consideration has been given to this problem of recirculation. By means of one such method, Gladstone (48) found in seven individuals a mean cardiac output of 5.4 l./min. which is higher than the values found by Grollman and almost exactly the normal mean of 5.5 l./min. obtained by Cournand (32) by direct cardiac catheterization. With this latter technic for direct comparison and with newer and possibly more precise technics for gas analysis now available the near future will probably see further developments in the estimation of cardiac output and pulmonary blood flow by study of inert gas exchange at the lungs.

C.) *Measurement of Blood Flow to Organs and Tissues*

A technic for the determination of cerebral blood flow in man has recently been developed (64, 72) which makes use of the principles of inert gas (nitrous oxide) exchange at a tissue. The equation for the Fick principle applied to a single organ (equation 8) may be integrated to yield an expression for the mean concentration of inert gas in the organ at any time, u, measured from the beginning of inhalation of the inert gas:

$$(C_i)_u = \frac{F_i}{V_i}\int_0^u (C_a - C_{v_i})\,dt \qquad (68)$$

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$$(C_i)_u = \frac{F_i}{V_i} \int_0^u (C_a - C_{v_i})\, dt \tag{68}$$

so that if C_i can be determined at any time and also the integrated values for concentration of the inert gas in arterial and venous blood from the organ, then the blood flow per unit volume of organ can be calculated. Without assuming instantaneous or even rapid diffusion equilibrium, it is nevertheless true, that if the time (u) over which the determination is made is sufficiently long, then, $(C_i)_u = \lambda_i(C_{v_i})_u$. At that time, then,

$$\frac{F_i}{V_i} = \frac{\lambda_i(C_{v_i})_u}{\int_0^u (C_a - C_{v_i})\,dt} \tag{69}$$

This principle can be applied to any organ for which it can be shown (i) that venous samples representative of all the venous drainage from that organ are obtainable, (ii) that there is negligible contribution to the venous blood sampled of drainage from other regions or organs than that under study, and (iii) that the experimental time period (u) is sufficiently long so that the inert gas tension in the venous blood sampled is representative of the mean tension in the organ itself. Evidence has been obtained (71, 72) that these conditions can be met in the case of the human brain. It is apparently also necessary (64) to point out that this principle does not require a constant arterial concentration and all the factors which go into that variable are conveniently eliminated by the simple expedient of measuring the arterial concentration throughout the determination and using the function so obtained in the calculation.

This technic has found successful application not only to measurement of human cerebral circulation (68) but also to the determination of coronary blood flow in dog (38) and man (10). Its application to other regions such as the extremities or the splanchnic area is beset with the difficulty that in such regions extremely slow components (resting muscle, fat) make the time of venous equilibrium impractically long.

In contrast to the technic above which yields a value for blood flow to an organ independently of diffusion factors are the methods which measure the time constants of uptake or clearance of inert gas (64) or other diffusible substances (67) in the various regions of the body. These depend first upon the assumption of constant arterial concentration of the substance in question, a condition which can be approximated by use of poorly soluble gases and hyperventilation (64) or local deposition of the tracer substance (67). In addition, however, in order to employ these time constants as quantitative measures of blood flow per unit volume of tissue it is necessary to assume instantaneous diffusion and the absence of arteriovenous shunts. Although such assumptions have been made and partially substantiated by Jones (64) who uses these constants synonymously with blood flow, it is not really necessary to take so bold a point of view. These uptake or clearance constants of diffusible substances measure a very important homeostatic function—the ability of the local circulatory and diffusion processes to supply substances to and remove them from the tissue cells. From the point of view of the local economy these overall constants are much more important than the quantity of blood flowing through the vessels.

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D.) *Application in Anesthesiology*

Since the volatile anesthetics behave like inert gases in the body, the principles of this exchange both at the lungs and the tissues are of fundamental importance to this clinical specialty (3, 52, 69, 118). Whatever the mechanism whereby an anesthetic gas produces its effects, there is little doubt that the intensity of those effects is directly dependent upon the concentration of the anesthetic in the tissues of the brain. Haggard (56) has demonstrated an excellent correlation between anesthetic level and brain concentration of ether as reflected in the concentration in internal jugular blood. A rigorous test of any theory of inert gas exchange in the body is its ability to explain the known differences in rate of induction and recovery among the anesthetics and the observed effects of changes in the various physiological parameters.

In an earlier part of this review, an expression (equation 52) was derived for the concentration of an inert gas in a tissue in terms of the factors which determine it. Thus cerebral concentration is dependent on cerebral blood flow per volume of brain, on factors of diffusion and solubility, and upon the past history of the arterial concentration of that gas. On the basis of recent experience (64, 66, 71), it may be stated that the factors of flow and diffusion in this organ are normally such as to introduce a time lag of the order of 10 minutes for the achievement of complete equilibrium between all parts of the brain and a certain arterial concentration of inert gas. It may be concluded, therefore, that the arterial concentration of anesthetic is the important determinant of rate of induction or recovery where this rate is slow (as in the case of ether); but where induction or recovery is rapid (as with ethylene), cerebral blood flow assumes considerable importance in addition to arterial concentration. Obviously, also, if the cerebral parameters are kept reasonably constant, as they would tend to be in a normal patient in the care of a competent anesthetist, the rise in brain concentration will depend almost entirely upon the shape of the arterial concentration curve.

In the section on theory, an expression was derived (equation 55) which described the alveolar concentration of a foreign gas as a function of time. Since one may assume, without serious error in the case of a normal individual, that the arterial inert gas tension is equal to that in the alveoli, this same equation also describes the shape of the curve of inert gas tension in arterial blood. It is seen that the alveolar curve appears as the sum of two terms, the first representing the process of lung washout, or the initial dilution of the inert gas by the residual gas and the pulmonary blood flow, the second representing the contribution of gas by the recirculating mixed venous blood. Since k_1 is quite large (never less than $\frac{M_A}{V_A}$ and therefore at least 1), this term represents an initial rapid rise toward some fraction of the inspired partial pressure. The remainder of the rise toward the inspired tension of inert gas in governed by the mixed venous blood tension and is a much slower process depending on blood flow, diffusion, inert gas solubility, and volumes of all the tissues of the body.

Thus the alveolar and arterial tension curves for any inert gas inspired at a constant partial pressure have three distinct phases (69): (i) an initial rapid rise occupying 3 minutes or less, (ii) a sharp inflection and (iii) a progressive slow rise reaching the inspired tension only after a period of hours. The rapidity of induction or recovery peculiar to each anesthetic is determined by the fraction of complete saturation or desaturation achieved in the initial rapid rise or fall of the arterial curves and this is given by the coefficient A_1 in equation 55. It is apparent that A_1 is quite sensitive to the solubility of the gas in blood and varies inversely with it. From the known values for λ, assuming normal values for M_A and F_p of 6 l./min. each, and neglecting diffusion lag across the pulmonary membrane, it is possible to estimate the fraction of complete saturation of arterial blood with inspired gas achieved within the first few minutes for each anesthetic, as follows (in order of decreasing value): ethylene 87%, nitrous oxide 67%, cyclopropane 68%, divinyl ether 42%, chloroform 12%, and ethyl ether 6%. This order is also one of decreasing rapidity of induction or recovery with each of the anesthetics named. Data have been reported for ether (56, 102), cyclopropane (100, 101), nitrous oxide (66), divinyl ether (103) and ethylene (95) which qualitatively confirm these predictions from the theoretical equation. There is need, however, for more such data obtained with a constant inspired tension, for all the anesthetics.

It is also possible to predict from equation 55 the effect of variation[illegible] in the physiological factors concerned on the shape of the arterial curve. Incre[illegible]ed respiratory minute volume will increase the height of the initial rise (A_1), especially where pulmonary blood flow or blood solubility is large, and will increase the rate of the whole arterial curve (k), especially where blood flow or solubility are low. This in general confirms the predictions and observations of Haggard (55, 58). Increased pulmonary blood flow will decrease the initial rise especially for soluble gases but will speed the rate of rise of the whole curve and thus shorten the time necessary for complete saturation or desaturation. Increased adiposity will slow the latter portions of the arterial curve especially for the highly fat soluble gases but will not significantly affect the initial phase of induction or recovery. For the effect of some of these variables see Figures 1, 2, 3.

In general, although theory seems capable of explaining many clinically observable facts, the applications of the principles of inert gas exchange to anesthesiology manifest the same tendency which is seen throughout all aspects of the inert gas exchange problem—a tendency for theory to advance far beyond empirically obtainable evidence. It is to be hoped that with the great number of physical technics now available some advance may be made in our comprehension of these phenomena, for intimately associated with them are the basic functions of the circulatory and respiratory systems.

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EXCHANGES OF POTASSIUM RELATED TO ORGANS AND SYSTEMS

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Recently a number of original studies and review articles (28, 31, 39, 50, 76, 77, 168) have served to focus the attention of the investigator and the clinician on the element potassium which, as a cellular and extracellular cation, accounts for about one half of the extra-skeletal fixed base within the body. In view of the diversity of the physiological processes and disease states encompassed in these various reports, it has seemed advisable to us to try presenting these data as they apply to various organs and systems. It is hoped that this will point out both knowledge and ignorance. Emphasis will be placed upon exchanges of potassium which occur between a) the organism and its external environment and b) the extracellular fluid and the cells. In view of the limited number and the accessibility of routes ordinarily involved in the external exchanges (gastro-intestinal tract, kidney, and to a much lesser degree, the skin), these balance sheets can be drawn with fair assurance. Much less certainty is present, however, in discussing changes which take place between cells, such as those of liver, muscle and nervous system, and the pericellular fluid since many of the estimates of transfers are indirect or inferred.

A. GASTRO-INTESTINAL TRACT

1. Exogenous potassium. Under ordinary circumstances potassium enters the body only through this route. It is present in practically all foods, being particularly high in animal and plant cells, including extracts of these such as bouillon, coffee and cocoa (15). Public water supplies usually contain only a fraction of a milliequivalent per liter. The daily intake of potassium may be zero in patients who are starving and in those given only selected clear liquids, or 100 milliequivalents or more in an adult laborer on a substantial diet. Analyses of animal and vegetable foodstuffs cited above indicate moreover that the amount of potassium ingested may vary considerably, depending on the soil in which vegetables were grown, the cut of meat, mode of preparation or preservation, etc. The oral intake may also be augmented by the use of "salt substitutes" which usually contain potassium. In animals, an excessive administration of this cation as an inorganic salt produces pylorospasm (215). In humans, anorexia, vomiting, diarrhea, abdominal discomfort as well as paraesthesias have been at times observed with the ingestion of KCl in multi-gram dosage (45, 212).

About four fifths of the ingested potassium is absorbed under ordinary circumstances at levels proximal to the large bowel. This is reflected in the relatively low potassium content of formed stools (61, 62, 77, 167).

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2. Endogenous potassium. Several lines of evidence indicate that body potassium may be lost via the gastro-intestinal tract. The invariable presence of this electrolyte in saliva and gastric juice, in duodenal and small bowel secretions, in pancreatic juice and in bile has been demonstrated (3, 94, 127, 145, 175, 176). It is of particular importance to note that these fluids frequently contain potassium in concentrations in excess of those which prevail in extracellular fluid, though lower than those present in the water of cells. This characteristic suggests that cells contribute potassium to these secretions.

It is obvious that the actual potassium concentrations encountered at any particular level in the gastro-intestinal tract will be influenced by the intake, if any, by the volume and composition of secretions, by the rate at which the contents move, and finally by the degree to which water and solutes are reabsorbed. It is not surprising to learn, therefore, that during periods of even moderate losses of such fluids to the exterior, as in diarrhea or vomiting, considerable deficits of body potassium can be incurred (39). Obviously the net losses will be all the greater in disease states which interfere with the ingestion and absorption of the usual potassium intake. This combination of potassium inanition and negative balances of body potassium has been studied in considerable detail in infants with diarrhea (48, 49, 97, 123, 200), in pyloric stenosis of newborns (41, 150), in adult patients representing a variety of gastro-intestinal disorders (8, 9, 108, 135, 192), as well as in diabetic subjects in acidosis or coma (25, 47, 92, 102, 103, 121, 148, 161, 163, 164, 177, 179, 185, 198, 201, 202, 206). The bulk of potassium lost comes from cells, either directly, as in gastro-intestinal tract secretions, or indirectly in replenishing extracellular supplies. Deficits may involve as much as one fifth of the potassium in the body. Evidence has been brought forth indicating that these losses may be of sufficient magnitude to jeopardize survival (86, 92, 100, 144).

Recognition of these exchanges of potassium between the body, the gastro-intestinal lumen, and the external environment has logically led to their use in removing excessive accumulations of body potassium such as those which occur in renal failure. The older approach of purging has not been revived, however, since it results in undesired losses of other body constituents such as sodium, chloride, water, etc. The same criticism applies as well to the use of small bowel lavage, though it is obvious that in both instances any inadvertent loss of extracellular or cellular constituents can be replaced by parenteral routes. With the latter technic such losses can also be avoided by the use of solutions of appropriate composition. A newer approach involves the use of cation exchange substances which can be administered orally. These include zeolites as well as sulfonic and carboxylic resins (27, 35, 36, 60, 158). The last of these has undergone the most extensive trials in human subjects (38, 44, 128). The H^+ or NH_4^+ cycle carboxylic cation exchange resin removes both exogenous and endogenous potassium with subsequent loss in stools. Since these exchanges need not involve specific cations, care must be taken to avoid depletion of sodium, either by replacement or by the use of a Na^+ cycle resin, alone or in combination with NH_4^+ or H^+ charged resin. Dramatic removal of accumulations of extracellular or cellular potassium by resin enema may also be achieved, although the effectiveness of this procedure varies considerably (64).

B. LIVER

The cells and the surrounding fluid of the liver represent a store of body potassium second in magnitude only to that in muscle. In several ways this organ can be looked upon as a way-station in the travels of both exogenous and endogenous potassium. Ingested potassium entering the portal system accumulates in the liver in increments which are higher than those recorded in other sites (129, 165). This appears to be related in part to the preferential position of this organ, anatomically speaking. This interpretation is bolstered by the demonstration that, with intra-arterial injections into one of the limbs, the greatest increases are those observed in the muscles supplied by the subdivisions of such a vessel (217). Further support for this point of view is available in the finding that injections of isotopic potassium into the antecubital veins produce maximal rises in cardiac muscle (37).

Evidence is available, on the other hand, that the liver participates in a more specific manner in the metabolism of this electrolyte. Thus, it should be noted that this tendency for potassium accumulation in the liver occurs even when this electrolyte is injected intravenously (63). Furthermore, potassium which is released during muscular contraction is in part taken up by the liver (75). Whether or not these are purposeful processes, it is clear that they do serve to temper any sudden influx of potassium into the extracellular fluid. If this is kept in mind, it is not unreasonable to suggest that the heretofore described congregation of orally given exogenous potassium in the liver may be more than fortuitous.

Published data indicate that deposition of glycogen in the liver is associated with a proportionate retention of potassium and other cations (74, 79). Furthermore, unavailability of these electrolytes in optimal proportions under *in-vitro* conditions results in less than maximal glycogen formation (109). Preliminary studies have indicated, however, that a complete absence of these electrolytes by no means abolishes the glycogenetic process in isolated rat diaphragm (183). Nonetheless it is obvious that the formation or the breakdown of glycogen is in general associated with increases and decreases, respectively, in liver potassium. Finally, though specific evidence is lacking, it is probable that, as in the case of muscle (*v. infra*), a protein-potassium ratio is present with gains or losses of potassium as the liver nitrogen content varies.

Certain studies do suggest, however, that this tissue does not always follow the pattern of potassium exchange characteristic of other tissues. Thus, desoxycorticosterone acetate (DOCA) administration does not produce depletion of liver potassium nor does adrenalectomy raise the liver content of this electrolyte (29, 52, 106). Also, the liver of potassium-depleted animals does not show the large electrolyte and potassium changes evident in muscles (113). With extensive hemorrhage, however, liver potassium is lost, presumably as a result of interruption of processes which maintain cell potassium levels intact (51).

C. MUSCLE

The bulk of body potassium is located within the voluntary muscles. This prepondernant distribution is related primarily to the mass of this tissue rather than to any unusual concentration of potassium in these cells. Actually, in view of the predominantly intracellular position of this ion, the cells of many other tissues and organs, including bone, contain potassium in levels much higher than those in extracellular fluid and as high as those in muscle (110, 146).

The mechanisms responsible for this disparate distribution remain as obscure as they were at the time the difference was first established. They are maintained by energy-linked processes, since with anoxia or death potassium pours out of cells (26, 56, 80, 81, 91, 211, 220). This fact, however, serves merely to confirm the reality of the difference rather than to trace its origins. The advent of isotopic potassium has served to establish that the potassium in cells is not absolutely segregated since it exchanges in a matter of hours with administered K^{42} (24, 104, 114, 129, 143, 165).

There are other observations which point to the transferability of potassium through membranes into or out of cells, including those in muscles. The occurrence of such migrations has been established in several ways for blood cells (40, 46, 57, 105, 137, 141). Similarly in muscle it has been shown, as cited earlier (75), that during contraction potassium is released from the cells and enters the extracellular fluid. The relative constancy of muscle potassium concentrations in itself is sufficient proof that a replacement of this lost fraction must subsequently occur. Losses of tissue potassium following operations (14, 16, 166, 172), during dehydration and starvation (10, 67, 69, 205, 210), diarrhea (86), vomiting (150), Cushing's syndrome (136, 208), or DOCA (53, 83, 140) or other steroid therapy (65, 88, 149, 182) result in reversible deficits of muscle potassium. It has been shown too that the entry of potassium into muscle cells may occur even when the stores of this cation are not depleted (78, 204, 218). Moreover, the lowered volumes of distribution of injected potassium salts in adrenalectomized animals or in humans or dogs with far advanced renal failure suggest that intracellular potassium concentrations are increased under these conditions (133, 216). This has been confirmed by muscle analyses (22, 29, 33, 52, 106, 156). Finally, the movement of potassium from extracellular fluids into cells in association with an attack of periodic paralysis provides another example of such transfers (42, 82, 99, 170, 187, 189). In this last entity it is not certain whether the muscle potassium stores are normal.

From the above observations it is clear that extensive transfers of potassium take place into and out of living tissue cells under a wide variety of physiological and pathological conditions, but the mechanisms by which these transfers are effected are not completely delineated. Experimental evidence has been adduced (19, 34) to support the theory that in skeletal muscle potassium passively diffuses into the cell to neutralize the nondiffusible intracellular anions, sodium being excluded. Since it was found that the extrusion of sodium is independent with respect to the time of entry of potassium and must perforce be an active transport against a high concentration gradient, even this theory makes the transfer of potassium dependent on energy-producing processes within the cell. From additional data (29, 33) it has been calculated that in the adrenalectomized animal potassium accumulates within the muscle cell as a result of the breakdown of anionic complexes which produce an increase in their electrostatic force. This change in the state of intracellular organic anions is associated with an increase in glucose-1-phosphate and a decrease in glucose-6-phosphate and fructose-6-phosphate, and is further evidence of the dependence of potassium exchanges on metabolic processes, especially the carbohydrate phosphorylation cycle.

Other experiments confirm this interdependence. It has been shown in the isolated living rat diaphragm that both glucose utilization and potassium uptake are increased by the addition of insulin (130, 207). It is not a reciprocal obligatory relationship, however, since, as mentioned previously, the absence of potassium in the external medium does not prevent glycogenesis in such a preparation (183). In intact rats, however, potassium depletion retards glycogenesis (98). Similarly in the cells of *E. coli* in which the major portion of potassium appears to exist as salts of hexose phosphate (17) potassium deficiency diminishes the incorporation of radioactive phosphate into phospholipids and nucleic acids in the presence of glucose, hexose phosphates, and other substrates (173). *In-vitro* studies (188) have shown that potassium conditions the reaction of actomyosin with adenosine triphosphate, but the exact mechanism by which this occurs is unknown.

It is customary to differentiate between movements of cell potassium occurring in conjunction with the anabolism or catabolism of protein and those in excess of such processes (1, 67, 69, 71). These subdivisions of the external and internal balances of this electrolyte are justified in view of the characteristic proportions in which K and N are lost from tissues during starvation (95). They point to the existence of potassium transfers independent of nitrogen metabolism. Studies of cation and water balances in various experimental and clinical situations have indicated a) that extensive transfers of potassium in excess of nitrogen may occur (41–43, 47, 49, 71, 102, 108, 124, 150, 169, 172, 192, 200), b) that frequently these are associated with reciprocal though not necessarily equivalent movements of sodium (34, 54, 66, 71, 83, 112, 152, 184), and c) that at times the base within cells (potassium as well as sodium) may vary in osmotic activity (70, 71, 203). Since muscle potassium makes up the bulk of the cellular phase of this electrolyte it is obvious that these processes will, from the quantitative point of view at least, occur preponderantly in this tissue. It should be pointed out that the failure to demonstrate alterations in the concentration of potassium in this or in other tissues does not disprove the occurrence of increases or decreases in this ion. Experimental evidence is available indicating that in the cellular phase. just as in the extracellular phase, concentrations may remain intact as a result of water movements, whereas the total amounts of potassium may be actually decreased or increased (156).

It has been claimed that in organisms that have reached a state of biological equilibrium (intact renal function) transfers of intracellular sodium and potassium bear a relationship to extracellular bicarbonate and chloride concentration

(54). In experimental animals, extracellular hypochloremic alkalosis has been associated with a movement of potassium out of, and sodium into, the intracellular phase of skeletal muscle, this relationship holding whether the alkalosis or the potassium depletion was initiated first (54, 97, 98). Hypochloremic alkalosis is a common concomitant of hypokaliemia and intracellular potassium depletion in many clinical conditions (8, 23, 41, 65, 66, 124, 135, 155a, 166, 172, 192). It is not clear just how this relationship is effected, and some evidence has appeared which suggests that intracellular sodium or chloride shifts are more directly involved than are those of potassium (66). In any case the mechanisms involved will not be clarified until a much more complete description is at hand of the exchanges of both cations and anions in each phase occurring under these conditions.

D. CARDIAC ASPECTS OF POTASSIUM METABOLISM

Though cardiac and skeletal muscles are histologically related, potassium exchanges in these two tissues are not necessarily identical. It has already been indicated that skeletal muscle changes need not be representative of those occurring elsewhere in the body, for example, in the liver. Some of the difference between the heart and other striated muscle may represent only analytical limitations. Others can be adventitious; thus, the higher uptake of K^{42} by cardiac cells following intravenous injection probably represents a geographical advantage. However, at this time no organ other than the heart is known to respond as dramatically to alterations in extracellular potassium. With moderate increases in plasma or extracellular potassium, increments of only 1 or 2 milliequivalents per liter above the upper limit of control values, the T wave of the electrocardiogram becomes peaked; later the QRS may become prolonged (191, 213, 214). As the levels rise toward 10–12 milliequivalents per liter the P waves are lost, the QRS contour changes to intraventricular block, and cardiac standstill supervenes before respiratory arrest. Blood pressure is maintained (119). This sequence of events, first delineated in experimental situations, is frequently duplicated, as will be mentioned later, in patients with anuria and less often in subjects with far-advanced renal failure with maintained or even increased urine volumes. It may also be seen in untreated diabetic coma and in patients given KCl (21, 101, 162, 186). The importance of this sequence of events in clinical situations cannot be over-emphasized, since preventative or remedial procedures are now at hand. Even without the complicated technics and apparatus of vivo-dialysis, a high carbohydrate-fat, *no* protein diet in renal failure or anuria will tend to prevent potassium intoxication. If elevated levels are already present, cation exchange resins will reverse the trend (44, 64).

On the other hand it has been shown that potassium deficiency induced in one of several ways produces histological evidences of myocardial and, in some species, skeletal muscle necrosis (53, 87, 139, 181). Cardiac enlargement and symptoms of congestive failure have been described in potassium-depleted patients (92, 96). The fact that mortality figures in infants ill with diarrhea can be favorably affected by potassium therapy (86) may be related to functional or histological sequelae in this tissue. It is not clear whether the S-T and T depression and the Q-T prolongation frequently associated with hypokaliemia represent alterations produced by decreases in the potassium outside of cells, inside, or both.

E. POTASSIUM AND THE NERVOUS SYSTEM

The cells of this tissue, in common with other cells in mammals, contain potassium in high concentrations. In spinal fluid, potassium concentrations are significantly lower than those in extracellular fluid (111). The significance of this disparity is not explicable by any known peculiarity of the extracellular-cellular phases of nervous tissue. It may be related, however, to the anatomical fact that the spinal fluid compartment is an analog of a bursa. Just as in other cells, adrenalectomy is associated with a rise in potassium in nervous tissue (115). Davenport, however, has indicated that in brain cells these changes do not take place, and that in this regard the brain, at least in rats, resembles liver in its behavior and contrasts sharply with skeletal muscle (54a). Another unusual feature of this organ is its ability to withstand the swelling of cells accompanying extracellular hypotonicity by releasing some of its own electrolytes (187a, 219).

Radioactive isotope distribution studies indicate that the penetration of tagged molecules occurs much more slowly in brain than in other tissues (165). This relatively slow interchange would suggest that acute phenomena associated with potassium administration are related to the peri- rather than the intracellular potassium. This view is in keeping with the paresthesia following potassium treatment (134), with the slowing of EEG observed with the injection of potassium as well as with the anti-curare (2, 18, 117, 122, 174) and perhaps the muscle anti-fatigue effects (120, 199) of injected potassium salts. In connection with this last group of studies it is of interest that hypokaliemia may mask hypocalcemic tetany (72, 73).

In common with the blood cell system, the loss of potassium occurring after incubation of brain tissue at body temperatures can be cancelled *in toto* by glucose in an anaerobic system and accelerated by fluoride (59). During aerobic incubation of brain slices this has been reported after glucose and l-glutamate but, following glucose alone, the suppression of potassium loss is only partial (194). Finally, perfusion of a local area of the cerebral cortex with high concentrations of potassium transiently raises its rate of oxygen consumption (55).

Extensive transfers of potassium and sodium across the membrane of nerve fibers occur in association with electrical activity in this tissue. By use of the radioactive isotopes Na^{24} and K^{42}, evidence has been obtained (116, 138) that during excitation of the giant nerve fiber of the squid, the phase of inward current is accompanied by entry of sodium and the more prolonged phase of outward current by a movement of potassium out of the fiber. This is not a simple exchange of the two ions by diffusion since these permeability changes are separated in time with the result that an action potential is produced during the cycle. Although sodium is moving down an electrochemical gradient during the initial phase, it must be actively transported against the gradient during the recovery phase. An expenditure of energy must therefore occur. It has been suggested

(160) that these sudden changes of membrane permeability are initiated by the local action of acetylcholine on the protein of the membrane. Electrolyte exchanges during excitation of this tissue are not restricted to peripheral nerves. Evidence of loss of potassium and gain of sodium by cerebral cortical neurones following convulsions induced in rats and rabbits by metrazol, electric shock, or sound has been obtained from micro-incineration and crystallographic analysis (30).

F. THE ROLE OF THE KIDNEY

The major role of the kidney in regulating the body fluids has been proven and emphasized repeatedly. Its importance in the excretion of potassium has been realized more clearly since the experimental demonstration that anuria following nephrectomy, ureteral ligation, and perhaps in some cases of $HgCl_2$ intoxication, results in death from potassium poisoning (118). More recent studies in patients with far advanced renal failure have indicated that even with continued urine output ECG changes and high extracellular fluid potassium levels appear in a minority of these subjects (68, 85, 131, 132, 147, 171, 180, 190). In the remainder, however, normal or even increased potassium excretion is encountered, sufficient at times to result in depletion (20, 23, 178). A number of studies provide reasonable explanations for this diversity of patterns. It has been shown in dogs that, either with an increased load of potassium presented to the kidneys for excretion or during an osmotic diuresis, there is tubular secretion of this electrolyte (12, 13, 89, 153–155). This finding makes it clear that potassium present in the urine can come from glomerular filtrate, tubular secretate, or both. It should not be surprising to find, therefore, that in nephron injury these two sources can be unequally affected, and as a matter of fact clinical data are available indicating that tubular secretion of potassium still occurs in chronically impaired kidneys (68, 142). This is based on the indirect evidence that in such subjects the glomerular filtrate, even when huge errors in the measurement of its rate of formation are assumed, cannot account for all of the potassium in the urine. This obviously need not be solely the result of activity of aglomerular nephrons, though such may be present.

Another function of renal tubules to be mentioned is the removal of potassium from glomerular filtrate (151, 157, 193). In view of the fact that water can only be abstracted but not added to the filtrate it is obvious that the occurrence of urine-plasma ratios of potassium lower than unity is evidence of "active" reabsorption of potassium. Though this is often cited as evidence for movement of potassium against a concentration gradient in plasma, a moment's thought makes it apparent this is not the case. Actually the initial transfer of the ion is against the high levels of potassium prevailing in cells, in this case, the proximal tubular epithelium (32). Hence *any* reabsorption of potassium which occurs when concentrations of this electrolyte in filtrate are lower than that in tubular cells must represent a transfer against a gradient.

These considerations raise important questions as to (a) the renal mechanisms involved in the excretion of potassium under maximal and minimal stimuli, and (b) the means by which the kidney interprets and responds to these stimuli. From the experimental work quoted above it is clear that active tubular reabsorption and active tubular secretion of potassium occur under minimal and maximal stimuli. It has been suggested that both mechanisms are active simultaneously in the excretion of a variety of substances, including potassium (6, 35). Although there are no unequivocal data as yet concerning the overlap of these two mechanisms between the two conditional extremes, the inhibitory actions of mercury on tubular reabsorption during water diuresis and on tubular secretion during potassium loading strongly suggest that filtered potassium is mostly reabsorbed and that facultative excretion is a secretory process (153).

Whatever may be the mechanism of the renal excretion of potassium in any particular instance, it is interesting to speculate on the way in which needs of the body for the ion are made known to the kidney. Under conditions of potassium deficit renal conservation may occur. It is hardly comparable to the abrupt renal conservation of sodium; urinary losses of potassium continue in the face of inadequate intake for many days (47), and reach a minimum only slowly, if at all (192). The stimulus does not appear to be simply the low concentration of potassium in plasma and extracellular fluid, since such low levels are often already present when the excretion rate is relatively high (192). Furthermore, the lowest urine-plasma ratios are observed after extracellular fluid levels have returned to normal (151). Likewise when potassium is administered in large amounts to potassium-depleted subjects and taken up by cells of the body, the renal excretion rate may not rise until several days after the plasma concentration has risen to normal or high levels (151, 192). These data suggest that the kidney responds to depletion and replenishment of potassium in the intracellular phase of tissues. It has been suggested that the specific site of stimulus may be either in the cells of the adrenal cortex (209) or in the renal tubule.

A similar interpretation is possible in regard to the stimulus for maximal excretion of the ion. Elevation of the plasma level is not the only correlate. Chronic dehydration is one of the strongest stimuli for the excretion of potassium (67). Under such conditions it is unrelated to the plasma level, filtered load, or rate of urine flow, and is accomplished at least in part by tubular secretion (155). These data again suggest that at least one stimulus to potassium excretion is the content or concentration of potassium in tissue cells.

G. ADRENAL CORTEX AND POTASSIUM METABOLISM

The accumulation of potassium in plasma, in extracellular water and in cells during adrenal cortical insufficiency (22, 29, 33, 52, 106, 107, 156, 221, 222), as well as the excessive urinary loss of potassium in extensive DOCA therapy (83, 84, 90, 93) or in Cushing's syndrome (159), has long since established the importance of this gland in the metabolism of potassium. Furthermore, clear cut morphological changes in the adrenal cortex accompany, at least in the rat, alterations in the potassium intake. Thus on a low intake of an inorganic salt of this cation the cortex is narrowed; with increased levels of intake it greatly increases in size with associated evidences of augmented secretory activity

(4, 5, 58). These alterations in form are accompanied by predictable changes in function. Thus urinary potassium losses rise with increased intake of this electrolyte and cortical hypertrophy, and under the opposite circumstances the converse is true. These alterations are presumably related to increases and decreases, respectively, in the secretion of DOCA-like steroids. It is of interest that these adjustments can occur in the absence of the anterior pituitary (11).

In view of these facts it would appear to be logical to assume that similar correlations exist during periods characterized by smaller fluctuations in potassium intake. If this be true, hormonal control of the urinary excretion of this cation can be postulated as a homeostatic mechanism. At present, however, there is no convincing evidence that any such precise relationship exists between the adrenal and its neighbor, the kidney. Despite this lack of direct evidence it should be emphasized that a variety of exogenous and endogenous steroids, the latter produced under the stimulation of administered ACTH, do modify the urinary excretion pattern of potassium. Whether the different effects which have been recorded, varying both in intensity and in direction, are the result of a direct action of any particular compound on the tubular epithelium or represent merely a secondary change is not known at present (7, 88, 125, 126, 149, 195–197). In behalf of the latter prospect it should be noted that a vast body of experimental facts is now being accumulated indicating that compounds with the steroid configuration do exert a variety of effects totally unrelated to adrenal function.

CONCLUSION

Potassium is a substance ubiquitous in living organisms. It plays a role in the physiological processes of nearly every type of tissue and organ; its pharmacological effects are legion. The wide scope of activities of this ion has been indicated by the experimental observations set forth in the foregoing pages.

The role of potassium in physiological processes is so extensive that this review is admittedly incomplete. Indulgence is begged for the fact that many papers have been either omitted from the review, inadequately criticized, or perhaps misinterpreted.

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THE INHIBITION OF GASTRIC SECRETION: A REVIEW

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Throughout the following review greatest attention has been directed to studies believed to have contributed most to current concepts concerning the inhibition of gastric secretions. But current concepts change and have personal bias. Investigations omitted now may be important later when new facts will open new vistas or reopen old ones. No escape is therefore offered to the investigator from the recurring task of reviewing source literature. This review will serve its greatest usefulness as a temporary vantage point from which to visualize future profitable lines of investigation.

MODES OF ACTION OF GASTRIC SECRETORY INHIBITORS

Gastric juice is usually produced by the action of secretagogues which are brought to the gastric mucosa via the blood stream or are liberated and act locally within the stomach or in the mucosa. These secretory mechanisms simplify the problem of the mode of action of inhibitors for when they are in operation inhibition of gastric secretion may be produced in two fashions; (1) by depression of the formation of the secretagogues and (2) by depression of the action of the secretagogues. Other modes of action may exist, but these simple mechanisms offer clear and direct approaches to the study of inhibition of gastric secretion.

Depression of Formation of Secretagogues. Reduced formation of secretagogues resulting in lowered output of juice may occur during the gastric and intestinal phases of the response to a meal whenever digestion or propulsion of the food is impaired. Also during the psychic phase of the response to a meal, influences which diminish or block vagal secretory impulses may also depress formation of the secretagogues in the mucosa and so limit the amount of juice produced.

The situation can become more complicated. The application of procaine to a portion of gastric mucosa can suppress its ability to form secretagogues without abolishing its ability to form gastric juice in response to secretagogues brought to it via the blood stream from other unanesthetized portions of mucosa (123).

Depression of Action of Secretagogues. Little is known regarding the depression of action of secretagogues. The site of action is "end organ" in type, the end organs in this instance being the peptic and parietal cells of the mucosa. Conceivably, these cells could be differentially affected by inhibitors; certainly they can be so affected by stimulants. It is possible that substances may depress the action of secretagogues by blocking their access to the cell or by combining in the cell with the substances with which the secretagogues normally unite. If these sites of union could be occupied firmly enough by a substance which itself did not produce secretion, reaction with the secretagogue could be prevented and secretion inhibited. It is not known, however, whether any of the inhibitors of gastric secretion act through such mechanisms.

General suppression of metabolism of the mucosa by nonspecific procedures, such as reduction of the supply of blood or oxygen or general cellular trauma, may depress the response of the mucosal cells to secretagogues, but in intact animals other tissues are likely to be affected before the gastric mucosa. The inhibition of specific enzymic reactions by specific compounds offers an avenue of approach which is more likely to lead to reduced production of specific ingredients of gastric juice and to a clearer understanding of the intimate metabolism of the secreting cell. Tests have been made of the effects of inhibitors of enzymes known to be present in gastric mucosa (75, 218). The approach is new and promising. It is limited at present by lack of knowledge of the enzymic mechanisms involved in the production of gastric juice.

Thus, gastric secretion may be inhibited through any of the many avenues by means of which it is stimulated or through any of the cellular mechanisms concerned with its formation. This complex pattern forms the background upon which the action of inhibitors is superimposed. The multiplicity of possible sites of action of inhibitors within this pattern is apparent and needs to be borne in mind especially when selecting methods for their assay.

METHODS OF DETERMINING GASTRIC SECRETORY INHIBITION

The method selected for determining inhibitor action will be the method which is expected to give the most exact and precise answer to the specific question under study. As a rule, the most decisive and interpretable results are obtained when the procedures used fulfill two requirements: (1) that the mechanism of the secretory process used to assess the inhibitor be understood and, if possible, that it be simple, and (2) that the method allows quantitative appraisal of the degree of action of the inhibitor.

In general, suppression of secretion may be assayed by measuring either changes in the threshold of secretion or changes in the amount and composition of secretion. With the first, comparison is made of the degree of stimulation necessary to initiate secretion when the effects of the inhibitor are present and when they are absent. This method has been neglected. It deserves further use, particularly because it represents an aspect of the action of inhibitors concerning which little is known. The strength of inhibitors' influences is most commonly determined by measurement of changes in the amount of secretion. Both procedures require the secretion of gastric juice and for this some form of stimulation is usually necessary.

Secretory Stimulation. In Response to a Meal. The secretory response to a meal has the advantage of being physiologic but the disadvantage of being complex. No investigation of an inhibitor's action is complete, however, without study of its effect on prandial secretion. If observations are to be made on the complete response to a meal, then the food used should contribute secretagogues during the chemical phases of the response. Foods vary considerably in their ability to stimulate this phase of gastric secretion (16, 242, 289). Meat or various preparations of meat were used extensively by Pavlov and his pupils more than fifty years ago for this purpose, and have been satisfactorily employed for it ever since (201, 242). When used to test the activity of an inhibitor, the meat has usually been given as a single meal (185, 231); occasionally it has been given in small, frequently repeated feedings (46). In either instance, an adequate number of concomitant control observations, free of the inhibitor's influences, are needed. One satisfactory procedure is to bracket the inhibitor test with control feedings done on preceding and succeeding days and to express the inhibition produced as per cent of the mean of the two control observations.

Test of the action of an inhibitor on the separate components of the response to a meal will allow more precise definition of its action and, as in the case of atropine, may aid in the elucidation of secretory mechanisms. To obtain psychic secretion for the elucidation of the mechanism of the inhibition produced by the ingestion of fat, workers in Pavlov's laboratory employed sham feeding of dogs with esophagotomies and gastrostomies (14*a* and *c*, 241*a*). Since then the procedure has been used satisfactorily many times by others (1, 80, 196). Great care must be taken to control the conditions of the tests if quantitative results are to be obtained. Nervous secretion induced by hypoglycemia after the administration of insulin (190–192) has been used for the same purpose (196). The secretory response of dogs to eating dry bread was found by Pavlov (241*b*) and Orbeli (237) to be almost entirely if not entirely due to nervous action. This simple mode of inducing nervous secretion might be very useful in studies of the action of an inhibitor and deserves further testing.

The secretion of vagally denervated pouches of dogs may be used to assess the strength of depressant influences on the humoral mechanisms of the chemical phases of the response to a meal. Secretagogues which may be liberated during psychic or nervous secretion are apparently incapable of stimulating the production of juice from mucosa upon which vagal secretory impulses are not acting (304). The Heidenhain type of pouch provides such mucosa and, when the food is placed in the appropriate organ, the gastric and intestinal phases of the response may be separated.

The humoral agent or agents involved in the gastric secretory response to a meal have not been identified with certainty (126). Gastrin and histamine are implicated (126, 154). Study of the action of inhibitors will be simplified when their exact roles in the secretory process have been identified. If gastrin plays the part in the secretory process assigned to it on the basis of accumulated knowledge, then its preparation in quantities sufficient to allow its widespread use would greatly facilitate the assignment of precise modes of action of inhibitors, as well as aid in many other physiologic and pharmocologic studies. Designation of the exact role of histamine in the secretory process would clarify the interpretation of existing data and make this substance a more precise implement in studies of gastric secretory inhibition.

In Response to Histamine. Of the secretagogues which are readily available and whose chemical composition is known, histamine has proved to be the most useful in studies of both secretion and inhibition. It has been used extensively in investigations on human beings, cats and dogs. Knowledge of its mode of action has been reviewed by Babkin (14*b* and 19*b*), Feldberg and Schilf (96) and Best and McHenry (31). It stimulates secretion from mucosa which has been deprived of its extraneous nerve supply (156, 180). At least a part of its action seems to be directly upon the secretory cells or upon structures or factors intimately associated anatomically with the secretory cells. This extreme peripheral action enhances its usefulness in studies of inhibition. So far, factors which have inhibited gastric secretion induced by histamine have also been effective or more effective in depressing secretion stimulated by other agents. The reverse has not always been true.

Histamine stimulates the production of a highly acid gastric juice. Its predominant and most clear-cut effect is upon the parietal cells. For practical purposes, it does not stimulate the mucous cells and the extent of its action on the peptic cells seems to depend somewhat upon the conditions of the tests (35, 50, 51, 108, 258, 317). In studies of action of an inhibitor it has been employed most often as a stimulant of acid gastric secretion.

In Response to Alcohol. Stimulation of gastric secretion by alcohol has been used in the assessment of inhibitors of gastric secretion (65, 113, 172, 189, 237). As a rule the alcohol is administered as a test meal. Successive tests result in a sufficiently similar output of juice (39, 182) so that quantitative determinations of inhibitor activity may be made. The mechanism by which alcohol stimulates gastric secretion is not known. It has been suggested that it does so through the liberation of histamine (89). If this proves to be the case, then alcohol will be useful in the search for an inhibitor which will depress the liberation of histamine without affecting its secretory action.

In Response to Vagal Stimulation. The effects of some inhibitory influences have been tested on gastric secretion induced by electrical stimulation of the vagi (23, 80, 241*c*, 304). The experiments are difficult and as a result vagal stimulation has usually been accomplished indirectly by the administration of parasympathomimetic drugs. Acetylcholine, acetyl-β-methylcholine chloride (methacholine) and pilocarpine have been most frequently employed. The effects of the choline esters on gastric secretion have recently been reviewed by Babkin (19*c*) and those of pilocarpine by Hollander (148). Their actions are complex and possibly reflect the varied actions of the vagus nerve itself. Pepsin, acid and mucous secretion are separately and sometimes differently affected. Inhibitory as well as stimulatory effects may sometimes occur (114, 233, 295). These factors combine to make the use of parasympathomimetic drugs difficult in tests of an inhibitor's action. When they have to be employed, as for example in the elucidation of the mechanism of action of an inhibitor (127), satisfactory quantitative data can be obtained only if the vagaries of their actions are kept in mind and adequate numbers of control observations are made.

In Response to Spontaneous Secretion. Spontaneous secretion is usually considered to be that secretion which occurs during the interdigestive period and for which there is no evident stimulus. Secretion of this type therefore has been ascribed to the inherent ability of the mucosa to secrete and is looked upon as a physiologic consequence of life in the mucosa! A more provocative viewpoint is that this secretion is produced through mechanisms which need elucidation. Carlson (1919) reported it as the "continuous" secretion of gastric juice occurring in human beings in the absence of food and evident psychic factors (55), and Lim (1924) later called it the "basal" secretion of the stomach in dogs (200). (In review, see Babkin 15 and 19*a*.) No matter what the cause of spontaneous secretion, it can be used for appraisal of an inhibitor's action if it is constant enough and if control tests are sufficiently reproducible. For practical purposes these requirements are fulfilled only in man and rats. In man night secretion or morning fasting secretion is usually used (177, 178) and in rats the secretion which collects in the stomach after duodenal ligation is regularly employed (100, 102, 286). Since the mechanism of spontaneous secretion is not established, the mode of action of the inhibitor may not be particularly clarified by the demonstration that it depresses the formation of this juice.

Tests of Inhibition During Intermittent and Continuous Secretion. The effects of an inhibitor may be assessed against an intermittent or continuous secretion of gastric juice. Intermittent secretion is usually induced by a single injection of histamine or other secretagogue. In practice, the complete response to each of two separate injections is usually followed; in the case of histamine the double histamine test is used, such as that first studied by Klumpp and Bowie (182). The inhibitor as a rule is given between the responses to histamine and often with the second histamine injection. The same procedure may be followed with other stimulants. The test, however, is particularly attractive with histamine because control responses to two successive injections of histamine are usually so similar (119, 168, 259). When used to appraise action of an inhibitor, however, the procedure has a number of disadvantages. Multiple tests may be necessary if the temporal characteristics of the action of the inhibitor are to be determined. Indeed, if stimulant and inhibitor are given simultaneously and the action of the inhibitor is delayed, it may be missed altogether; or, if the inhibitor is given with the first injection some remnant of its action may be present after the second. Maximal inhibition is likely to occur only if the maximal effect of the inhibitor coincides with the period of greatest stimulation by histamine. Also, during the response to a single injection of histamine the output of juice per minute increases quickly to a peak and then declines rapidly. The inhibitor, whose onset of action may differ from that of histamine, may have different depressant effects on different rates of secretion. These factors may combine to make repeated quantitative determinations difficult. Double and triple histamine tests, however, are simple and quickly performed, and once the temporal characteristics of an inhibitor's action are known, the tests can often be usefully employed.

Assay of an inhibitor's action against continuous secretion of gastric juice eliminates many of the objections to the intermittent tests. Gray, Bradley and Ivy (115) introduced the procedure. They gave histamine subcutaneously in fixed doses every ten minutes. In dogs such injections produce a plateau of secretion which is maintained almost constantly for many hours if the injections of histamine are continued (59, 115). When a steady state of secretion is developed the inhibitor is given and the injections are continued. By this method the precise temporal relations of the inhibitor's action may be noted (38, 126). The time of its onset of action and its period of maximal effect are clearly evident, and the time of release of the cells from its depressant influence is obvious if the tests are continued long enough.

Relationship of Rate of Secretion to Amount of Inhibition. With the use of histamine as a secretory stimulant, Gray, Bradley and Ivy (115) noted that the degree of inhibition produced by enterogastrone was dependent, in part at least, upon the rate of secretion at the time of testing. Uniform doses of enterogastrone produced greater inhibition at slower rates of secretion. Other investigators also used histamine as the secretory stimulant and found a similar relationship when determinations were made of the inhibition produced by extracts of gastric mucus (59). The observations indicate that if quantitative determinations of the inhibition produced by these and other preparations with similar actions are to be repeated with similar results, then the rate of secretion per unit of gastric mucosa must be the same or comparable in all tests. Code, Blackburn, Livermore and Ratke (59) have accomplished this, at least in a rough fashion, in a method they have devised for use in dogs with Heidenhain pouches. The maximal rate of secretion of acid possible from each pouch in response to histamine is first determined and then when the potency of the inhibitor is to be assessed, a rate of secretion which represents a definite proportion of the maximal rate is used. In this way similar states of physiologic activity per unit of mucosa are obtained in each dog independent of the animal's size or the size of its pouch. With uniform doses of an inhibitor, much greater depression of secretion occurred at slow rates than at fast rates of secretion. For example, at rates which were 25 per cent of the maximum the inhibition was complete, while at rates which were 50 per cent of the maximum the inhibition was only about 60 per cent complete. Indeed, the amount of inhibition produced remained the same at rates of secretion in excess of about 40 per cent of the maximum.

A relationship between degree of inhibition and rate of secretion has been demonstrated only when histamine is used as the secretory stimulant and when enterogastrone or extracts of gastric mucus are used as inhibiting agents. The action of other depressants may not be so dependent upon the rate of secretion and a different relationship might be found with other stimulants. Study of the relationship is, however, one method of gaining insight into the mechanism of inhibition and for this reason it should be an important consideration in all tests of depressant influences.

Special Features of Different Species Employed in Tests of Inhibition of Gastric Secretion. Most studies on inhibition of gastric secretion have been carried out on human beings, dogs, cats or rats. There are limitations to the results obtained with each. Their seriousness depends somewhat on the objectives of a study. Consideration of the limitations relative to each species may aid in devising experiments which give decisive answers to questions under study.

Human Beings. The major detriments in determinations of the activity of an inhibitor are the errors which may arise as a result of incomplete or contaminated collections of gastric juice from human beings. If the inhibition is calculated upon the basis of output of acid or pepsin, and this is usually the most satisfactory way to express the results, then collections of juice during the tests must be complete. Losses into the duodenum, even if they are constant during the control period, may be increased or decreased by the action of the agent under investigation and lead to false indications of stimulation or inhibition. Contamination with secretions from above the stomach also may alter values of volume and of acid. Much has been done to overcome these difficulties. Continuous removal of the juice from the stomach by constant suction and careful expectoration by the patient of all secretions collecting in the mouth have enabled investigators to carry out repeatable quantitative assays (177). Double histamine tests, secretion in response to alcohol, continuous secretion and responses to a meal have all been used. In the first three procedures the collections generally represent pure gastric juice but in the fourth the problem arises as to what to do with the samples containing food. If the food is removed the mucosa is being deprived of stimulant. If it is replaced, escape of juice into the duodenum is bound to occur and collections will be incomplete and irregular (182); then the assay must be based on changes in the concentration of pepsin or acid and not on changes in their output. One group of investigators has solved the problem, in part at least, by not starting the tests until one hour after feeding, when much of the meal has passed out of the stomach; the stomach is then emptied and continuous collections of juice are started. A plateau of secretion is obtained which probably represents the later phases of the secretory response to the meal and upon this plateau tests of inhibitor activity can be superimposed (98).

The major advantage of studies on human beings is that the action of inhibitors in this species is usually of greatest practical importance as well as interest.

Dogs. The major advantages in the use of dogs are (1) complete collections of juice are possible and (2) the animals may be studied in the unanesthetized state. Complete collections of juice are made from the entire stomach or from pouches of the stomach draining only to the exterior. The preparation of pouches from different portions of the stomach with complete nerve supply or in various stages of denervation, affords a means of precisely delineating the site of action of an inhibitor. Also, a variety of tests may be done by use of different secretory stimuli. These facts make the dog the most completely satisfactory animal now available for use in the investigation of inhibitor agents.

Cat. Studies on inhibition of gastric secretion in cats have been carried out mainly with the animal under anesthesia. This introduces a complicating factor because the anesthesia may alter the action of the inhibitor, and check determinations are difficult to make on unanesthetized members of this species. Nonetheless, cats seem to be particularly suitable for studies in which gastric secretion is produced by direct stimulation of nerves (23, 304). Anesthetized cats also give reproducible responses to histamine. These reponses may be satisfactorily employed for assay of action of gastric secretory inhibitors (150, 305).

Rat. The "Shay rat" was introduced by Shay, Komarov, Fels, Meranze, Gruenstein and Siplet (286) as a simple preparation in which gastric ulceration quickly occurred and which they believed could be readily adapted for use in assays of antacids and antiulcer agents. Their anticipations were correct for their procedure has been adopted by others and now is widely used in determinations of both antiulcer and antisecretory factors (102, 240, 257, 314). The procedure is based upon the observation that fasted, lightly anesthetized rats submitted to pyloric ligation have a more or less continuous secretion of gastric juice which persists for many hours (100, 184, 286). Determinations of secretory inhibition are made by comparing the amount of juice obtained from a series of treated animals with that obtained from a control series.

It has been stated that the continuous secretion obtained from the rat under these circumstances is caused by nervous stimulation because it is eliminated by vagus section or atropinization and reduced by deep narcosis (286). The observations are important and need expansion for if they are substantiated the usefulness of the method will be increased further, since some specificity of action could then be ascribed to an effective inhibitor and the procedure employed in studies aimed at the mechanism of inhibition.

Final Comment Regarding Methods for Determining Secretory Inhibition. Methods employing antiulcer effects for measurement of antisecretory activity have not been discussed. Antiulcer effects may be due to factors other than secretory inhibition (267). No matter what method of testing is used, results obtained from one species cannot be applied without qualifications to another species for at present it is not clear to what extent the action of inhibitors may differ from one species to another. Quantitative studies aimed at this question should yield significant information. Likewise, it is exceedingly difficult at present to make integrated interpretations of results obtained by different methods. Quantitative comparisons of the inhibition produced by similar dosages of depressants in the various procedures now available are greatly needed.

CLASSIFICATION OF GASTRIC SECRETORY INHIBITION

The causes of gastric secretory inhibition may be classified as physiologic, pathologic or pharmacologic. They are discussed in this order herein because inhibition by pharmacologic means may involve physiologic and pathologic mechanisms.

PHYSIOLOGIC GASTRIC SECRETORY INHIBITION

Basal Secretion. Basal secretion collected from dogs and human beings has usually been that obtained at night or in the morning, after a meal the preceding noon or afternoon (149, 177, 200, 273). Some of this secretion is therefore likely to be prandial in origin. Studies are needed after more prolonged fasting. No matter what the cause of basal secretion its presence or absence may affect the response to secretagogues. Lim (200) found in dogs that the total acid output after administration of histamine represented the sum of the basal secretion plus that evoked by histamine. Dependence of the secretory response of human beings on basal rate has been observed (202). It was found that persons with low basal rates did not secrete as much or as concentrated hydrochloric acid in response to the injection of a standard dose of histamine. Studies are needed to determine whether or not the presence or absence of basal secretion affects the threshold amount of different stimuli. Is priming of the secretory mechanism advantageous when attempting to obtain maximal responses to single fixed intensities of secretory stimuli? With some drugs it is (233, 262). Conversely, are there factors related to basal secretion which could be brought into play to reduce the response to stimulation? It has been noted casually by a number of workers with whom the author is associated that a forty-eight-hour fast reduces the responsiveness of Heidenhain pouches in dogs to standard doses of histamine, and it also has been noted that the susceptibility to stimulation varies in different types of gastric pouches. Casual observations in our laboratory, however, have been notoriously misleading in the past! Although considerable work has already been done on the factors controlling basal secretion, additional systematic studies are needed on the relation of basal secretion to the susceptibility of the mucosa to stimulation.

Acid. Pavlov (241*d*) reported that accumulation of acid in the stomach during digestion ultimately prevented the further secretion of gastric juice. His pupil, Sokolov (294), observed that in dogs with gastric and duodenal fistulae, and with Pavlov pouches and stomachs disconnected from the duodenum, inhibition of secretion from the pouch occurred when 0.5 per cent hydrochloric acid solution was introduced into the stomach or when gastric juice was introduced into the duodenum. These early observations have been confirmed and extended. The inhibition is apparently excited by contact of acid with gastric or duodenal mucosa, although in some studies, particularly some of those on human beings, the influence of these two regions could not be separated because acid was often placed in the stomach without prevention or determination of its passage into the duodenum. Also, the objective of studies in which acid was placed in the stomach was often not a search for inhibition of acid secretion but rather its neutralization or dilution. Many of these investigations therefore lack control tests and as a result, from the point of view of inhibition, their results are not decisive. When specific tests have been made of the effects of acid in the duodenum on secretion in the stomach, clear-cut results have been obtained (81, 244, 284). In normal animals and human beings acid in the duodenum is an effective inhibitor of the secretion of acid by the stomach.

Most types of gastric secretion are inhibited by acid. The acid used is not a determining factor since similar results have generally been obtained with hydrochloric, sulfuric, acetic and butyric acids (18, 94, 110, 217, 307, 308). The concentration, however, is important. Little inhibition has been noted in the stomachs of human beings and dogs until strengths of acid of 0.03 (282) and 0.08 (325) normal, respectively, are used or until the pH of the duodenal contents is less than 2.5 (244).

Fasting, continuous or basal secretion in pouches of dogs is unaffected by acid in the duodenum (244) but is somewhat diminished by instillation of acid directly in the pouch (94, 110). In human beings, acid placed in the stomach may reduce fasting secretion (28, 217) particularly if the concentration of the acid is high (282).

Psychic or nervous secretion incited by sham feeding (81) or insulin (244) and the first hour of the secretory response of a Pavlov pouch to feeding (244), which is predominantly nervous in origin, are all definitely inhibited by acid in the duodenum, the inhibition ranging from about 30 to 60 per cent. Acid introduced into the stomach instead of the duodenum may not be as effective although lack of control tests makes it impossible to express the results quantitatively (323).

The secretory response to the ingestion of a meal in human beings is suppressed by placing acid in the duodenum (125, 284) or in the stomach (8, 217, 307), but since some of the acid may have passed into the duodenum the site of origin of the inhibition in these tests is not known. In dogs the gastric phase of the secretory response to a meal may be reduced by contact of acid with gastric mucosa (110, 325) or by acid in the duodenum (244). The intestinal phase of the response to a meal is decisively and uniformly inhibited by acid in the duodenum (81, 244, 322), but may not be affected by the presence of acid in the stomach (322). Acid in the stomach seems to be effective only in inhibiting prandial secretion when the meal and the acid are in contact with the same mucosa. For example, an acidified meal always produced less acid from a pouch of most of the stomach when the meal was placed in the pouch (322) while acid in a pouch did not much affect the secretion of that pouch when it was being stimulated by a meal in the main stomach (110). The results suggest that acid may inhibit the release of secretagogues in the mucosa.

Stimulation of gastric secretion by alcohol is inhibited in human beings by acid placed in the stomach (217) or in the duodenum (125). When the stimulus is histamine, in the dog at least, acid in the stomach (324) or in the duodenum (244) has no effect on the response. Since alcohol may cause gastric secretion by liberating histamine, there is again the implication that acid may produce some of its inhibiting effect by diminishing the formation of secretagogue in the mucosa. Some intermediate mechanism must be in action when acid in the duodenum is suppressing secretion in the stomach. Search for an inhibitor in the juices secreted as the inhibition develops is indicated. Only the circumstances under which inhibition by acid occurs have really been determined; little is known of the intimate mechanisms involved.

Nervous Inhibition of Gastric Secretion. Two means of producing gastric secretory inhibition through nervous channels are theoretically possible: 1. Inhibition could be produced by increasing the number of impulses passing peripherally to terminations whose stimulation would lead to reduced secretory output by the gastric mucosa. This would be an active process of peripheral inhibition produced by stimulation of inhibitory nerves or their terminations. 2. Inhibition could be produced by reducing the number of impulses reaching terminations of nerves whose stimulation leads to the production of gastric juice. Secretion excited through nervous channels would then be reduced and possibly the secretory reactivity of the mucosa depressed. This would be a process of inhibition produced by suppression or the blocking of secretory impulses. It could conceivably arise anywhere in a reflex arc producing gastric secretion, in the end organ of the afferent nerve or the afferent nerve itself, or centrally or peripherally in the efferent nerve or its terminations.

Stimulation of Vagus Nerve. Due to the long latent period of fifteen to sixty minutes or more preceding the secretion of gastric juice which occurred when he stimulated the vagus nerve directly, Pavlov thought there were inhibitory as well as secretory fibers in the nerve (241*e*). This latent period has been shortened to seven to forty-two minutes (312), three to five minutes (141) and fifteen to twenty minutes (44) by modifications in the method of stimulation and control of the loss of carbon dioxide which apparently occurred in Pavlov's dogs as a result of forced artificial respiration used in his laboratory (18). While these latent periods may still be rather long, they certainly cannot be taken as indicative of secretory-inhibitory fibers in the vagus. They simply keep the question open and suggest that the problem might be attacked in another fashion. For example, weak electrical stimulation of the vagus nerves has been observed to stimulate mucous secretion (23, 312), stronger stimulation being necessary to produce acid. A search, with various types of stimuli, might reveal inhibitory effects such as a raised threshold of the acid secreting cells of the mucosa while mucous secretion was being stimulated.

Stimulation of Sympathetic Nerves. From a review of the literature and a presentation of some of his own experiments Bickel, in 1925 (33), concluded that the sympathetic nervous system provides both secretory and inhibitory fibers to the gastric mucosa. The sympathetic secretory fibers, he stated, were concerned with the secretion of the solids in the juice. It is established now that electrical stimulation of the sympathetic nerves supplying the stomach causes a secretion of a mucoid juice, particularly from the antrum, which is low in enzyme activity (23, 141). Whether or not sympathetic nerves carry gastric secretory-inhibitory fibers was not decisively settled by the evidence presented by Bickel in 1925 (33) nor has it been settled since. For example, basal gastric secretion may be reduced in volume (141) and its acidity raised (141) or lowered (23) and the secretory response to histamine may be reduced or unaffected (24) by electrical stimulation of the splanchnic nerves. The bulk of the evidence indicates that increased mucous secretion occurs during stimulation of the splanchnic nerves. The changes observed, however, have always been small and the experiments often complicated by anesthesia, acute operative procedures, degenerating nerves (315) and inductional methods of nerve stimulation. The problem needs re-exploration in healthy unanesthetized dogs with the more subtle methods of stimulation of nerves now available.

Extirpation of Nerves. 1. Vagotomy. Pavlov decisively demonstrated that bilateral vagotomy abolishes the secretory response of the stomach to sham feeding (241*f*), and that avoidance of psychic, oral and esophageal stimulation when food is placed directly in the stomach results in a delayed and reduced output of juice (241*g*). These observations were extended in his own laboratory (237) and have been amply confirmed by subsequent investigators (5, 6). Today it is agreed that vagotomy abolishes gastric secretion caused by stimulation of the vagus nerve. Does resection of the vagi do more? The gastric secretory responses of patients with peptic ulcer and of dogs with innervated pouches of the entire stomach to injections of standard doses of histamine are reduced by vagotomy (65, 236, 297). The patients also show a reduced gastric secretory response to alcohol test meals and a reduction in continuous night secretion after vagotomy

(58, 236, 297). The twenty-four-hour output of gastric juice by dogs with pouches of the entire stomach is also suppressed by section of the vagi (327, 328). These tests, however, are superimposed on somewhat abnormal conditions. Patients with peptic ulcer may be unusually resistant to the inhibitory effects of acid in the duodenum (284). Dogs with pouches of the entire stomach are denied this mechanism for the suppression of their gastric secretion, a fact which may contribute to their high twenty-four-hour output. Possibly under these conditions the mucosa may be more easily stimulated than normally. The results already cited definitely demonstrate that vagotomy reduces the responsiveness of such mucosa to histamine. But does the operation do more under these circumstances than simply restore mucosal excitability to normal? In dogs with pouches of the entire stomach it may not, for the threshold dose of histamine, when pouches of the entire stomach are vagally denervated, has been found to be the same as in intact animals (131). Decisive tests of excitability before and after vagotomy under uncomplicated conditions, for example, in dogs with the newer types of innervated gastric pouches (124, 148a, 162, 301), have apparently not been made. Orbeli (237), as long ago as 1906, felt that his tests indicated a reduced excitability of the mucosa after vagotomy. His vagotomy, however, included separation of the pouch from the stomach, and interruption of enteric continuity may have affected his results. This factor, common to studies in Heidenhain pouches, and that of lack of acid in the duodenum, common to studies of pouches of the entire stomach, would be avoided by use of the Jemerin-Hollander type of innervated pouch (124, 163, 301). The results would be more certainly quantitative than those obtained in dogs with gastric fistulas, in which the animals' gastric secretory responses have already been found to be reduced by vagotomy (7).

2. Sympathectomy. There is no doubt that anesthetization or removal of the splanchnic nerves produces little or no lasting change in the secretion of gastric juice of human beings or animals (24, 141–143, 152, 226, 290). Temporarily, spontaneous secretion of mucus may be increased and the response to sham feeding reduced. The acidity of the juice secreted in response to a meal may be increased (142, 143, 226), but the changes reported are small and the vagaries of the tests used are great. It seems safe therefore to conclude that preganglionic sympathectomy does not have significant lasting effect on gastric secretion. Quite different results might be obtained if the effects of postganglionic sympathectomy were tested. This suggestion is based on the observation, first reported in 1903 (247) and later amply substantiated (106, 198, 204, 302), that removal of the celiac and superior mesenteric ganglia in dogs is followed by a severe watery, bloody diarrhea and in some of the animals by the development of typical peptic ulcers in the stomach and duodenum. Failure to induce these findings may be due to incomplete removal of ganglia and postganglionic fibers, for in the most recent studies (198, 204), when the celiac, superior and inferior mesenteric ganglia and the nerve fibers extending along associated vessels were removed, the results were consistent. Reports have not been found of the effect of this procedure on gastric secretion in otherwsie innervated pouches. The re-

sults might show whether or not there are fibers in the sympathetic nerves supplying the stomach which can inhibit secretion or change mucosal excitability.

Central Inhibition. Bickel and Sasaki (34) observed a decisive diminution in psychic secretion induced in a dog by sham feeding when a cat was brought into the presence of the dog. The dog was enraged and frustrated and in the two experiments reported the response to sham feeding was reduced 86 and 89 per cent. Others have induced emotional upsets in human beings under hypnosis and have observed prompt inhibition of psychic secretion (146) and the secretory response to a meal (27). The dimensions of the problem have not been thoroughly charted. For example, does inhibition which involves a central nervous mechanism produce its effect only by reducing the number of impulses passing down secretory fibers of the vagus nerve or can it also alter the secretory response of the mucosa to other stimuli?

Continuity of the Enteric Plexus. Hou and Lim (149) found consistently higher basal secretory rates in pouches with intact or partially intact enteric connections to the main stomach than in pouches which had been completely separated from the stomach. Isolation of pouches from the stomach, which interrupts continuity of the enteric plexus, is a factor often lost from sight in studies of gastric secretory function. It is generally agreed that motor impulses spread along the gut through the enteric plexuses. It is not known whether the presence of food in one portion of the stomach can incite secretion in another portion simply by spread of impulses along enteric nerve plexuses in the wall of the stomach. The factor needs study in relation to the responses of different types of pouches. For example, when a pouch is separated from the stomach, continuity of the enteric plexuses as well as central vagal connections are lost. The part which the loss of enteric continuity may play in the altered responses of such a pouch has not been assessed.

Exercise. The secretory response of a Pavlov type of pouch in a dog to feeding is reduced by moderate or strenuous muscular work (42, 64, 250). Psychic secretion induced by sham feeding is also suppressed (250). Similar effects have been observed in human beings (135, 136, 276). The inhibition is accompanied by a reduction in gastric motility (134, 137) and the suppression of gastric secretion in the studies enumerated could therefore be caused by reduced vagal secretory stimulation combined with reduced liberation of secretagogues caused by the interruption of motility and digestion. Additional factors, however, may be involved. Secretion stimulated by alcohol is depressed by exercise (138); that induced by histamine has been found to be reduced (197, 276) or to be unchanged (138). A suppression of responsiveness of the mucosa itself may be involved. Thus although the origin of the inhibition is admittedly central, whether or not the efferent channel is solely vagal and its mode of action entirely one of suppression of secretory impulses is not settled. Tests in vagotomized animals seem indicated.

Fat and Enterogastrone. Complete and excellent reviews of the physiologic aspects of the inhibition of gastric secretion by fat and enterogastrone are available (126, 157, 251). Only some basic facts and considerations which might be helpful from a pharmacologic point of view need be summarized here.

Fat. Ewald and Boas (93) in 1886 were the first to show that the ingestion of fat inhibits gastric secretion. They added olive oil to a test meal and observed suppressed secretion of acid and delay in passage of the meal from the stomach. Pavlov and his pupils some years later decisively demonstrated the inhibitory action of fat by quantitative studies in dogs with pouches and various fistulae (14*a* and *c*, 241*a*).

Site of Action. The main inhibitory effect of fat on gastric secretion originates in the duodenum (241*a*). Fat confined to the stomach has little or no inhibitory action as compared to fat placed in the upper portion of the intestine (201, 211, 293). This is also true of the inhibitory effect of fat on gastric motility (254, 316)

Types of Secretion Inhibited. Nervous secretion in response to sham feeding or injection of insulin is reduced or abolished by fat in the duodenum and nervous secretion in response to a meal is delayed, suppressed and often prolonged (196, 241*a*, 283). Basal and prandial secretion is inhibited in dogs with vagotomized pouches of the entire stomach (159). Tests on secretion induced by histamine have given more variable results (2, 3, 261, 283). There is some suggestion that the variability may depend on the size of the dose of histamine in relation to the amount of fat placed in the duodenum and the period between the instillation of the fat and the administration of the histamine. Strong stimulation by histamine and pilocarpine may, after an initial delay, break through the inhibitory influence of the fat (2).

The volume of the juice, the output of acid and the concentration of pepsin in the juice are all decisively reduced by the ingestion of fat. The fall in concentration of pepsin is often striking (2, 3, 241*a*, 283).

Mechanism of Inhibition. Pavlov and his co-workers held the view that the inhibition involved a nervous mechanism, the interposition of a nervous reflex between the duodenum and the stomach (14*a*, 241*a*, 293) with the vagus nerve playing a decisive role (237). Their tests, however, did not settle the problem. Evidence accumulated during the years from 1920 to 1929 showed that a humoral factor or factors must be involved.

Lim, Ivy and McCarthy (201) demonstrated that mechanically induced gastric secretion in vagotomized stomachs which were separated from the esophagus and intestines was inhibited by fat in the duodenum. The vagus nerves did not participate in this inhibition. The participation of a humoral mechanism in the suppression of gastric secretion and gastric motility was proved by Feng, Hou and Lim (97) and Farrell and Ivy (95) when they showed that the ingestion of fat inhibited the secretion (97) and the motility (95) in a totally denervated autotransplanted pouch. The autotransplanted pouch was stimulated to secrete by the ingestion of a meal and its inhibition might have been due, in part at least, to reduced formation of secretagogues in the remaining gastro-intestinal tract. Also, in such preparations the nerve connections between the duodenum and the main stomach are usually intact and an inhibitory hormone could conceivably have been liberated from this portion of the stomach by a reflex operating between it and the duodenum. That such mechanism is not necessary for the inhibition of gastric motility by fat was settled when Quigley, Zettelman and Ivy (254) found that fat introduced into the duodenum inhibits gastric motility in vagotomized pouches of the entire stomach and other more completely denervated stomach pouches, the only significant difference from intact animals being that the onset of inhibition was somewhat delayed in the denervated preparations. Separation of vagal influence from the secretory inhibitory effects of fat has not been as complete. For example, inhibition of the secretion of pepsin by fat does not occur if the vagi are severed (128). Whether or not an inhibitory reflex between the duodenum and innervated portions of the stomach is ever involved in the inhibition of the secretion of acid by fat is not settled, but the fact that the formation of gastric juice in a completely denervated pouch in response to direct mechanical stimulation is suppressed by fat establishes beyond any doubt the participation of an inhibitory agent which circulates in the blood. This agent may be enterogastrone.

Enterogastrone. Once participation of a humoral mechanism in the inhibition by fat was recognized, extracts of the bowel were soon tested and found to possess inhibitory effects (185, 186, 188). In 1930, the name "enterogastrone" was appropriately suggested by Kosaka and Lim for the active principle in these extracts (185).

Action. The effects of purified preparations of enterogastrone may be summarized as follows. In dogs, the volume, the acid output and usually the acid concentration of all of the types of secretion so far tested, from pouches of portions or all of the stomach, with nerve supply intact or in various stages of denervation, are decreased by the intravenous injection of extracts of enterogastrone. Cephalic secretion in response to sham feeding or insulin, the response to a meal and that to histamine or pilocarpine are all inhibited in dogs (115, 128, 188, 196). Continuous secretion is diminished in the rat (102, 314). Extremely large doses are apparently required to reduce secretion in human beings (98, 177, 178, 194, 246), and conflicting results have been obtained when preparations of enterogastrone have been given to anesthetized cats in which gastric juice was secreted in response to histamine (150, 305).

Differences between the effect of extracts of enterogastrone and the action of fat in the duodenum have been demonstrated. For example, preparations of enterogastrone are much more potent inhibitors of secretion induced by histamine (115) and have much less effect than fat on the secretion of pepsin. In fact, the concentration and output of pepsin are sometimes increased after injections of enterogastrone (128). Fat in the upper protion of the intestine inhibits motility in the denervated stomach (254) while enterogastrone does not inhibit the motility in a stomach with all nerve connections severed (187) or in one with its vagal nerve supply sectioned (132). Extremely large doses of enterogastrone are needed to inhibit gastric secretion of human beings (178); on the other hand fat in the duodenum is very effective (283). Enterogastrone has been given intramuscularly to human beings, and this may account for its comparative ineffectiveness. Ultimately these differences may not be important, but they require resolution before the conclusion can be drawn that the activity found in intestinal extracts is the hormone, enterogastrone, whose existence is supported by such strong physiologic evidence. The problem seems to rest largely with the chemical purification of the active ingredient and this has proved to be a most difficult task.

Carbohydrate in the Duodenum. The stimulating prospect pharmacologically lies in the answer to the question, Can pharmacologic agents be found which will specifically excite the liberation of enterogastrone or excite an enterogastric inhibitory reflex? Drugs with this specific action have not been reported. Yet, other substances have effects similar to those of fat. As reviewed earlier, acid in the duodenum inhibits gastric secretion. The ingestion of concentrated solutions of glucose or large amounts of other carbohydrates depress the secretion and delay evacuation of the contents of the stomach of human beings (225) and dogs (80, 99, 219, 252). The effects are due to the presence of sugar in the duodenum and not to an elevated concentration of blood sugar or to the presence of sugar in the stomach (253, 285). In the dog the inhibition of motility by carbohydrate, like that by fat, is independent of the nerve supply of the stomach (285). Gastric secretion stimulated by nervous means, for example by sham feeding and by administration of insulin and pilocarpine, is decisively inhibited (80, 99, 219), while gastric secretion after the administration of histamine is less effected (80).Thus other agents besides fat can excite an enterogastric inhibitory mechanism. A pharmacologic agent with this specific action is needed.

Pregnancy and Urogastrone. Towards the end of 1939 three groups of investigators became interested simultaneously in the gastric secretory inhibitory activity of urine. Sandweiss and his co-workers became interested through their discovery that extracts of urine from pregnant women had a beneficial effect on ulcers produced in dogs by the Mann-Williamson operation (43, 270); Gray, Wieczorowski and Ivy, through their intense interest in enterogastrone and the prospect that the active ingredient in the urine might represent excreted enterogastrone (117); and Necheles and his collaborators through the possibility that hormones of the gastro-intestinal tract, like those from some other sources, might be excreted in an active form in the urine (231). From this trilogy has sprung our present knowledge of substances in urine which affect the gastrointestinal tract.

The prevention of ulcers in Mann-Williamson dogs by urinary extracts was pursued particularly by Sandweiss and his co-workers. Such prevention was soon found to occur with administration of extracts from nonpregnant women (266, 271) and to be due, not to the inhibition of gastric secretion, since with the doses used depression was not observed (26, 269, 271) but to another factor believed responsible for the prevention and healing of the ulcers which Sandweiss has named "anthelone" (266). Gray and Ivy and their collaborators pursued particularly the factor in urine which inhibits gastric secretion. This they soon named "urogastrone" (121), and the source, action and pharmacologic possibilities of this factor are particularly pertinent to this review.

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Urogastrone. Urogastrone has been found in extracts of urine from normal human beings and dogs and in the urine of pregnant women (103, 104, 117, 118, 231). It is demonstrable in the urine of patients with peptic ulcer (103), gastric cancer and pernicious anemia (101), although the amount in the urine of patients with peptic ulcer may be less than that found in the urine of normal persons (120). Purified preparations of urogastrone are the most potent inhibitors of gastric secretion so far tested. Doses of less than 1 mg. reduce the secretory response of dogs to histamine (122). Cephalic and prandial secretions are also suppressed (101). Biliary and pancreatic secretion are unaffected and no immediate changes are produced in salivary secretion (122). Gastric secretion stimulated by histamine in cats (150), guinea pigs and pigeons (101) and that which occurs after duodenal ligation in rats (102, 151) has been reported to be reduced. In man, basal secretion and that induced by histamine are suppressed by subcutaneous injections of urogastrone (320). One preparation of urogastrone given intravenously to two patients caused reactions in both and reduced the free acidity of the gastric juice in one (268). The intimate mechanism by means of which urogastrone suppresses the formation of juice in the gastric mucosa is not known. It seems to act directly and with some specificity on gastric mucosa. Once its chemical constitution is known, other related compounds will certainly be tried and it is hoped a more easily prepared substitute will be found.

The Relationship Between Urogastrone and Enterogastrone. Although the attractive prospect that urogastrone represents excreted enterogastrone was at first entertained (117), and some preliminary evidence in support of the possibility was uncovered (70), it later had to be abandoned, in part at least (120). The question of whether or not any of the gastric secretory depressant action of urinary extracts is due to excreted enterogastrone is still unsettled. It is present in the urine of dogs after gastrectomy and duodenectomy (101, 104), and although the amount in the urine is apparently reduced by enterectomy, some is still present (120). One limited conclusion at least is warranted from these results; if the small bowel is at all a source of the gastric secretory depressant activity in urine, it is not the only one (120). Lack of quantitative methods of extraction of urogastrone have hindered these investigations (120) and, as emphasized currently by Grossman (126), further clarification of this relationship awaits their development.

Urogastrone and the Endocrine Glands. Oophorectomy in dogs may reduce the amount of urogastrone in the urine (168, 169) while thyroidectomy is without effect (169). Kaulbersz, Patterson, Sandweiss and Saltzstein have made two studies of the effect of hypophysectomy on the urogastrone content of the urine. In the first (167, 168), the urine of two hypophysectomized dogs was found to contain little or no inhibitory action on gastric secretion when determined by their assay procedure. They used a double histamine test in dogs with Heidenhain pouches or gastric fistulas but they usually gave the urinary extracts with the first injection of histamine. The control, and in this case the second injection of histamine, was given three hours after the first test was completed or about four and a half hours after the injection of urogastrone (167, 168). In the sec-

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Urogastrone and Pregnancy. The prospect of a relationship between pregnancy and the occurrence of a gastric secretory depressant in urine was one of the origins from which knowledge of urogastrone has sprung. Recently its study has been neglected, although there are ample data to more than justify its further exploration. For example, as long ago as the late twenties and early thirties it was shown that the concentrations of acid and pepsin of women were usually low during pregnancy and nearly always rose after delivery (9, 298). Administration of emmenin, which was originally an extract of human placenta, was found in 1937 to produce a slight reduction in the volume of juice obtained in response to histamine from two patients with duodenal ulcer (12). Anterior pituitary-like hormone, prepared from pregnancy urine (antuitrin-S and follutein), was given subcutaneously or intramuscularly in doses of 1000 to 5000 units to five female dogs with Pavlov pouches for five consecutive days. They produced a reduction of the volume and of the free and total acid of the juice secreted in response to test meals in four of the dogs (68, 69). Other tests, however, in which "antuitrin-S" has been given in single daily subcutaneous or intramuscular injections have given negative results in dogs and human beings (271). The inhibitory action of three proprietary gonadotropic hormone preparations on gastric secretion has recently been tested in our laboratory in dogs with Heidenhain pouches secreting at rates of more than 40 per cent of the maximum in response to repeated doses of histamine (unpublished data). When given intravenously two of the preparations showed inhibitory activity. Reports of quantitative comparisons of the twenty-four-hour output of urogastrone in the urine of pregnant and nonpregnant women have not been found in the literature. It would be interesting to know if pregnancy alters the amount. Again, lack of a quantitative procedure has no doubt blocked such studies. Despite this lack all evidence so far accumulated indicates a close association between urogastrone and the chorionic gonadotrophic hormone excreted during pregnancy. Similar methods have always been used for their extraction (70, 101, 121). That they are not identical chemically was clearly demonstrated by early work (122), but that they are closely related chemically is decisively supported by the recent studies of Huff, Risley and Barnes (151). There is a definite possibility that the tie between these active substances stems from membership in the same family of chemical substances (151). Crude concentrates of urogastrone appear to be mucoprotein in character (122). Highly purified preparations contain carbohydrate (151). A mucopolysaccharide with protein or polypeptides attached to make a big molecule, as indicated by the work of Huff, Risley and Barnes (151), or with few or no such attachments, to make the smaller molecule indicated by the detailed study of Gray, Wieczorowski, Wells and Harris (122), would bring the purified urogastrone products isolated by these two groups of workers into the same family of compounds, that is, the mucoproteins or glycoproteins, and would orient urogastrone with the mucoproteins of chorionic origin (151, 223). But enough of such schemes. The evidence for such chemical relationship is decidedly sketchy and consideration of their prospect is justified only if it leads to extensions of knowledge in this perplexing field. A mucopolysaccharide has not been identified in urogastrone and until it has no conclusions can be drawn.

Mucus and Gastric Secretory Inhibition. Brunschwig and his co-workers, in a series of papers published during the years 1939 to 1943, reported finding a gastric secretory depressant in gastric juice of human beings and dogs (45–49, 280). The juice from patients to be tested for secretory depressant activity was secreted in response to histamine and that from dogs was obtained after feeding. Assays of action of the inhibitor were made on dogs with subtotal, wedge or Heidenhain types of gastric pouches. The pouches were stimulated every ten to forty minutes by small feedings of meat. In the first group of reports the juice to be tested was simply neutralized and then injected intravenously (45, 46, 48). Later, acid extracts were made of normal and cancerous gastric mucosa from human beings. These were neutralized, suspended and injected intravenously (45, 47). In the final studies of the series, precipitates of gastric juice were prepared by the addition of sufficient ethanol to bring the concentration to 80 per cent. The precipitates were collected, mixed with water or saline solution and, after suspending any undissolved material, were injected into the test animals (45, 49, 280).

In the earlier studies when the neutralized juice only was used, definite inhibition of secretion was produced most frequently by the injection of achlorhydric juice from patients with pernicious anemia or cancer of the stomach (45, 46, 48). About 70 to 90 per cent of these tests showed activity of an inhibitor. Results of only about 17 to 20 per cent of the tests were positive when acid gastric juice was used. When achlorhydric juice from patients without pernicious anemia or cancer of the stomach was used, 28 per cent of the tests had positive results (46). Juice from normal dogs showed no activity (48). When the alcoholic procedure was used, however, gastric secretory inhibitory activity was found much oftener in gastric pouch juice of dogs, human acid gastric juice and achlorhydric juice of patients without pernicious anemia or cancer (49). Alcoholic precipitation allowed concentration of the material and the doses of juice and precipitate used routinely favored the precipitate (1 cc. untreated juice per kilogram of body weight compared to precipitate from 10 to 30 cc. of juice given to dogs weighing 6 to 10 kg.). Yet, the finding of activity in precipitates from types of juice in which it had not been noted when untreated samples were used suggests that the alcoholic procedure may have enhanced the activity.

The qualitative methods employed in the assessment of the activity and the lack of quantitative procedures throughout the studies make comparisons difficult and possibly misleading. For the same reasons, the actual amount or concentration of the activity in the different types of juices cannot be stated. It appeared, however, to the investigators, and their data certainly support such a contention, that the inhibitory factor was present in highest concentration in the achlorhydric gastric juice of patients with pernicious anemia and carcinoma of the stomach (280). Their position in this regard was strengthened somewhat by the results of their tests for activity in their extracts of gastric mucosa and gastric cancer. About half of the extracts of the cancers or the mucosa from achlorhydric stomachs showed activity of an inhibitor while the incidence with extracts from normal mucosa was about 19 per cent. Their results definitely indicate that a gastric secretory depressant may be present at times in acid gastric juice of human beings and dogs more frequently and possibly in greater concentration in achlorhydric juice of patients with pernicious anemia or carcinoma of the stomach. Its concentration, however, is not related to the hydrogen-ion concentration of the juice (179). Caution in interpretation is necessary. Besides the lack of quantitation in the assay procedure, reactions seem to have occurred rather frequently after injections of the juice, the extracts and the precipitates. The data presented do not include precise statements of their severity or incidence. When they occurred it is highly probable that they contributed to the secretory inhibition. Nonetheless, the studies are interesting. They have opened a new approach to a difficult problem and judgment of their validity must await accumulation of more data.

Recently, a group of workers stimulated by the results obtained by Brunschwig and his collaborators reopened the search for a gastric secretory depressant in gastric juice. They first attempted to develop a more accurate method for the quantitative determination of the action of a gastric secretory inhibitor. This has been accomplished (59). Continuous secretion of gastric juice at known rates from Heidenhain pouches in response to histamine forms the background against which the strength of the inhibitor is assessed. By means of this method Blackburn and collaborators (37) determined the inhibitory activity of alcoholic precipitates of achlorhydric gastric juice from patients with pernicious anemia, of achlorhydric juice from otherwise normal individuals and of acid gastric juice from normal persons. All of the assays were done at secretory rates in excess of 40 per cent of the maximum. Doses of 10 mg. of precipitates from the achlorhydric juice of the patients with pernicious anemia produced, on the average, 71 per cent inhibition; doses of 25 mg. of the precipitates from the achlorhydric juice from otherwise normal persons were required to produce the same degree of suppression while doses of 100 mg. of precipitates from acid gastric juice showed either less inhibitory activity or none at all. The results confirm the general findings of Brunschwig and his co-workers and, in addition, show that the active factor is capable of inhibiting secretion induced by histamine.

In a search for the source of inhibitory activity in the alcohol precipitates, commercially available gastric mucin and pepsin of hogs were tested (36). None of the preparations of pepsin so far employed have shown any inhibitory activity. A similar result was obtained by Atkinson and Ivy (12) when they gave pepsin subcutaneously. Most of the preparations of hog gastric mucin so far tested have been active. The inhibition obtained is proportional to the dose administered (265) and is present even if only the soluble material extractable from the mucin is given. Because of the rather drastic acid treatment used in the preparation of hog gastric mucin for commercial purposes, tests were carried out with fresh gastric mucus obtained immediately after killing hogs. Simple saline solutions of this material produced definite secretory inhibition and the activity was completely precipitated by 80 per cent ethanol (61). The results have prompted a search for inhibitor activity in other mucigenous secretions, particularly saliva, since some of the mucus in the stomach is no doubt derived from this source. Brunschwig and co-workers gave human saliva to dogs intravenously (45) and in some instances observed secretory suppression. Redissolved alcoholic precipitates of saliva produced some inhibition though less than that obtained with comparable amounts of fresh gastric mucus of hogs (61). Alcoholic precipitates of canine gastric juice also have been found to contain activity (205). A search has been initiated for a possible stimulant of inhibitor secretion from the gastric mucosa (60). Methacholine was tested because of its auto-inhibiting and mucous stimulating action when given repeatedly (114, 295). Juice obtained after its injection had a higher content of inhibitor activity than juice secreted in response to histamine (205).

A close association was indicated between the gastric secretory inhibitor activity and mucus, particularly in cases in which fresh mucus was scraped from the surface of the hog's stomach, diluted and the soluble portion promptly given to a dog used for assay. Treatment with alcohol precipitates the mucus and the activity accompanies the precipitate. As in the case of urogastrone, a search for a mucopolysaccharide, a mucoprotein or a closely related family of such compounds with similar activity is indicated.

But again a note of caution must be sounded. In six of the last seven reports just cited, mention is made of reactions which may accompany the intravenous injection of preparations of mucigenous materials. While the reactions do not always occur they are noted sufficiently frequently to force investigators to await clarification of the mechanism of the inhibition and the role which the reactions may play in its production before assigning even a tentative function to this type of gastric secretory inhibition. Search for the active factor may lead only to the door of the culprit producing the reactions!

Changes in Circulation. The multiple sources from which the stomach receives its supply of blood have made determinations of flow of blood to the organ difficult and have retarded the accumulation of knowledge regarding the relation of flow of blood to gastric secretion and inhibition. Excellent studies on the isolated perfused stomach have been made and these have shown that, within wide limits, gastric secretion occurs independently of flow of blood (202*a*). For example, in these studies the pronounced vasodilatation and increased flow of blood caused by sodium nitrate was unaccompanied by stimulation of secretion and even when the blood flow was steadily diminishing the secretory response to histamine continued (202*a*). While it seems likely that pronounced vasoconstriction and diminished flow of blood may affect gastric secretion the precise contribution which they may make to the development of inhibition has not been assessed in intact unanesthetized animals. (For further data see sections on epinephrine and posterior pituitary extracts.)

PATHOLOGIC GASTRIC SECRETORY INHIBITION

During the course of pharmacologic or physiologic studies of the inhibition of gastric secretions, the injection of crude extracts or even pure compounds may produce reactions of an abnormal nature and these may cause inhibition of gastric secretion. Should their occurrence be missed, the inhibition they produce may be falsely assigned. Their importance, therefore, to investigations of gastric secretory inhibition cannot be overestimated.

Nausea. Pavlov recognized that cephalic secretion or that related to appetite was reduced in distracted or distraught dogs, and since his time it has been generally appreciated that "unappetizing" experiences may diminish psychic secretion. But few experimental studies of factors having an emotional association or content have been made (see discussion of Central Inhibition), and it has not been generally recognized that other types of gastric secretion also may be affected. The two best reports dealing specifically with the effects of nausea and vomiting on gastric secretion are those by Atkinson and Ivy (11) and Grossman, Woolley, Dutton and Ivy (129). In the first, emetic drugs were used. Their effects were tested on dogs with Pavlov pouches and patients with duodenal ulcer. Fixed doses of histamine were used as the secretory stimulus. The subcutaneous injection of 6 mg. apomorphine hydrochloride combined with 36 mg. codeine sulfate produced vomiting accompanied by a reduction in the response to histamine of about 50 per cent in volume and 30 per cent in acid output. Intravenous administration of 120 mg. of emetine hydrochloride produced vomiting and diarrhea and stopped secretion entirely; 65 mg. decreased secretion of acid by 30 per cent. It is not stated whether or not this dose induced vomiting. A combination of 15 mg. of morphine sulfate and 6 mg. of apomorphine were given by subcutaneous injection to the human beings. Although the maximal concentration of acid secreted in response to histamine was the same as in control tests, the secretion declined more rapidly and the total output was less. The complete suppression of secretion by the larger dose of emetine deserves consideration by all those testing drugs or extracts of biologic material.

In the study by Grossman and co-workers (129) nausea was induced in six dogs with vagotomized pouches of the entire stomach and two with subcutaneously translated pouches of the fundus and vagotomized pouches of the remainder of their stomachs. After preliminary tests in these animals a preganglionic sympathectomy was performed, thus depriving their pouches of all ordinary connections with the central nervous system. Nausea, salivation and retching were induced by drawing a balloon over the esophageal duodenal anastomosis a number of times while the pouches were secreting continously in response to repeated injections of histamine. The procedure inhibited secretion of all of the pouches. The results indicate that a humoral agent is involved in the production of the inhibition. The humoral factor might have arisen at the site of irritation by the balloon or from some other area not included in the denervation which was excited through an esophageal reflex originating above the esophageal-duodenal anastomosis. The inhibition produced was decisive. The inhibitory potency of factors which produce nausea, vomiting and retching is impressively displayed. The potential danger of masking the visible signs of nausea, salivation, vomiting and retching by anesthesia should always be considered if assays of an inhibitor's activity are to be made in its presence.

Fever. The first thorough tests of the effect of fever on gastric secretion were made by Meyer, Cohen and Carlson in 1918 (222). Dogs with Pavlov pouches which had been fed a test meal of meat were used in all of their experiments. In some cases forced feeding was necessary. Two sets of experiments were performed. In the first, fever was induced by the intravenous injection of killed cultures of *Bacillus prodigiosus* or 10 per cent solutions of sodium nucleate. Most of the dogs had diarrhea, mucous and bloody stools and some had severe chills and prostration after the injections. Body temperatures rose from control values of 101 to 102° F. to temperatures of 103.7 to 106.1° F., and an inhibition of secretion of about 60 to 90 per cent occurred. In the second set of tests a rise in body temperature was induced by use of a fever cabinet. The body temperature was elevated from maximal control levels which were less than 102° to values ranging from about 103° to 108° F. The volume and total and free acidity of the juice were greatly reduced or secretion was abolished. Factors other than just the fever often seem to have been involved. The injection of foreign materials usually produced toxic effects besides raising the body temperature, and the animal's sojourn in the fever box may sometimes have been a distressing experience capable of inducing some central inhibitory influences. No experiments were reported in which the dogs were put in the box without inducing fever.

By means of intact, vagotomized or splanchnicectomized dogs in which gastric analysis was carried out by oral intubation, Vanzant and Snell (310) found that the intravenous injection of killed cultures of *Bacillus prodigiosus* usually produced a rise in body temperature of 4° F. or more and a marked reduction in the secretory response to histamine. These results have been extended recently in a quantitative study of the effect of purified pyrogens on gastric secretion in dogs with pouches of the entire stomach (38). The pyrogens were given while the pouches were secreting continuously in response to repeated injections of histamine. The pyrogens used were pyromen, prepared from cultures of *Pseudomonas aeruginosa*, and pyrexin, prepared from sterile exudates induced by turpentine in the pleural cavity of dogs. Both preparations produced definite gastric secretory inhibition only when a rise in body temperature occurred. There was some association between increase of temperature and the amount of secretory inhibition, but as much inhibition was sometimes produced by increases of 1° as occurred with elevations of 3° to 4°. It is possible that the pyrogenic preparations contained mucoproteins and that some fundamental chemical reason exists for the simultaneous presence of pyrogenic activity and secretory inhibitory activity in these extracts. The mechanism of the secretory inhibition produced by pyrogens is not known. Would it affect isolated perfused gastric mucosa, the temperature of which could be kept within normal limits? In this regard, the experiments of Necheles and co-workers are pertinent. They found that subpyrogenic doses of pyrogens can cause inhibition of gastric motility in dogs (234) and may also affect secretion (228). The co-existence of secretory depressant and pyrogenic activity in the same compound or in a group of closely related compounds is worth setting up as a temporary hypothesis to be tested by further experimentation.

The most careful study of the effect of fever on gastric secretion in human beings is that of Bandes, Hollander and Bierman (22) which also includes a review of the earlier clinical literature. They tested the effect of elevations of body temperature to peaks of 102° to 106.1° F. produced by use of a fever cabinet. Whenever a high fever was induced and continued for more than three and a half hours a transitory anacidity occurred during which stimulation by alcohol was ineffective. The authors could not find a satisfactory explanation for the temporary anacidity. No matter what the mechanism involved may be, it is clear that gastric secretory inhibition often will accompany fever and this alone dictates the necessity of frequent checks of body temperature during all tests of inhibitory activity.

Anoxia. It was shown many years ago that gastric secretion was diminished in dogs when they were transported to high altitudes (25, 82). The problem has been carefully studied in dogs with Pavlov and Heidenhain pouches by Van Liere and collaborators. They have found that the volume, total acidity and pH of the juice secreted in response to a test meal of meat are reduced by exposure of the animals to partial pressures of oxygen ranging from 94 to 63 mm. of mercury (243). Dramatic changes were produced by partial pressure of 63 mm. of mercury only, which corresponds to an altitude of 28,000 feet. The basal secretion obtained fifteen to nineteen hours postprandial from Pavlov pouches was affected little by oxygen want within ranges compatible with consciousness in unacclimatized dogs (311). The results obtained for human beings have been somewhat conflicting. One group of observers has noted that degrees of anoxemia which markedly suppressed activity of the cerebral cortex and came close to paralyzing vital centers caused little or no inhibition of gastric secretion (139). Other workers have observed diminution in the volume and acidity of juice at a simulated altitude of 5000 meters which ordinarily would produce some signs of cerebral anoxia (165). The possibility of psychically induced inhibition must be borne in mind when interpreting the results of all these studies. It is clear from them, however, that anoxia must be severe before dramatic reductions in gastric secretion occur, and that the gastric mucosa can secrete acid even when the amount of oxygen contained in the blood is greatly reduced.

Metabolic Disturbances. Hypercalcemia. Elevation of the concentration of calcium in the blood depresses gastric secretion. This was decisively demonstrated by Babkin, Komarov and Komarov (21) in 1940. Subsequent reports by Babkin and his pupils have extended the original findings (17, 111, 278). Hypercalcemia induced by the intravenous injection of calcium lactate, the administration of parathyroid hormone or activated ergosterol inhibits the gastric secretory response of dogs to feeding. The nervous phase is particularly affected, responses to bread, sham feeding and injections of insulin being seriously reduced (17, 21). Secretion induced by histamine may be unaffected (21) or slightly reduced (17) by parathyroid hormone and more definitely affected by injections of calcium (111). The main effect of a high concentration of calcium, however, is a depression of the nervous mechanisms of gastric secretion, possibly both centrally in the nervous system and peripherally in the nervous tissue of the stomach.

Hyperglycemia. Prolonged hyperglycemia of patients with diabetes may be accompanied by a reduction of the acidity and volume of the gastric juice. (For a concise review of the clinical literature, see references 80 and 285.) Experimentally, the intravenous injection of large quantities of glucose has been found to suppress gastric secretion in cats and dogs (80, 99, 196, 219, 235) and human beings (285). If sufficient amounts of glucose are given, all types of secretion so far tested can be affected. If 4 to 5 gm. per kilogram of body weight is injected intravenously into dogs (196), or 8 to 9 gm. per kilogram of body weight into cats (235), gastric secretion in response to histamine is reduced while lesser quantities of sugar may fail to counteract its action (80, 99). Nervous secretion provoked by sham feeding is very susceptible (80). In human beings, the intravenous injection of 10 per cent solutions of glucose can produce some inhibition of gastric secretion in response to feeding (285).

The mechanism of the inhibition has not been clarified. Hypertonicity of the solutions given may be an initiating factor, but regardless of whether or not it is the sugar or the hypertonicity of its solution which initiates the response, the inhibition itself may originate centrally in the nervous system or peripherally in the mucosa. Some preliminary experiments indicate that section of the vagus nerves may diminish the inhibition (99). These deserve extension.

Deficiency of Vitamin B Complex. Deficiency of vitamin B complex produces another situation in which carbohydrate metabolism may be disturbed and gastric secretion inhibited. As high as 50 per cent of patients with pellagra may have achlorhydria, and it may also occur in some cases of beriberi (164, 321). Webster and Armour gave a vitamin-free diet to dogs and observed first a marked diminution and later a disappearance of the secretion of gastric juice in response to sham feeding, alcohol placed in the intestine or histamine injected subcutaneously (318). The normal secretory responses of the animals to these stimuli were restored by feeding powdered yeast (318) but not by giving cod-liver oil (319). Cowgill and Gilman (63) produced a marked diminution in the response to histamine from Pavlov pouches in each of three dogs fed a diet deficient in vitamin B complex and mainly in vitamin B_1. In one dog, a true achlorhydria developed. There was no change, however, in the secretory response of a Heidenhain pouch in a fourth dog given the same diet. Dogs with Heidenhain and Pavlov pouches which were fed another diet (Goldberger's diet number 195) known to produce black tongue failed to produce any change in the secretory response to histamine. A difference between deficiency of thiamine and niacin is indicated. It should be pointed out that these experimental studies were carried out before the components of the B complex had been decisively separated. More specific deficiencies could now be produced and these might yield interesting results. A recent study in the mouse supports this possibility. Davenport and Jones (79) have found that the excised stomachs of thiamine-deficient mice show a reduced ability to utilize pyruvate and to secrete inorganic acid.

Besides offering new approaches to the problem of gastric secretory inhibition these investigations serve to alert those studying secretory inhibition to the necessity of maintaining a high and uniform nutritional status in all animals used for assay purposes.

Miscellaneous Factors. Increased Intragastric Pressure. It has recently been shown in anesthetized dogs that when the intragastric pressure is elevated to 35 or 40 cm. of water the secretion of hydrochloric acid in response to histamine ceases (260).

Acidosis. The intravenous injection of hydrochloric or lactic acid in dogs in amounts sufficient to reduce the carbon dioxide combining power of the plasma to less than 30 volumes per 100 cc. will reduce the secretory response of the gastric mucosa to electric stimulation of vagus nerves (44). Even greater reductions in the carbon dioxide apparently must be present before secretion induced by histamine is affected (44).

Mucosal Irritation. It was demonstrated in Pavlov's laboratory that the instillation of a 95 per cent solution of alcohol into the gastric pouch of a dog results in the secretion of alkaline mucus with extremely low digestive power, accompanied by a diminution of normal secretory activity (277). It is now well known that strong irritants applied to the mucosa lead to the secretion of mucus (94, 292), but the effect which this has upon the gastric secretory response to physiologic stimulants has not often been studied. Necheles and Meyer have shown that the instillation of oil of peppermint in Heidenhain or Pavlov pouches suppresses their response to small or moderate doses of histamine but usually has little effect on their response to large doses (229). Atkinson and Ivy (12) found that frequent gastric lavages with irritating solutions of silver nitrate or sodium selenite for a month or more increased the amount of mucus secreted and reduced the secretory response of the mucosa to a meal and to histamine (12). Once again there is an association between mucus, mucoprotein and gastric secretory inhibition. Tests for an inhibitor of gastric secretion in the mucus secreted in response to irritation might aid in the elucidation of the mechanism of this interesting phenomenon.

Ionizing Radiations. It has been demonstrated repeatedly in dogs that exposure of the gastric mucosa to roentgen rays or gamma rays of radium produces a variable and temporary reduction in gastric secretion (57, 160, 163, 224, 249, 291). Careful study has established that an adequate dose of roentgen radiation always depresses the gastric secretion of human beings, frequently to the point of achlorhydria, but the effects are variable, temporary and unpredictable (238). In a recent study Simon (287) found that exposure of the mucosa of Heidenhain pouches in dogs to the radioactive isotope of phosphorus was followed, in a few days, by a decrease in the concentration of hydrochloric acid and the volume of the juice secreted by the pouches in response to histamine. All five animals which he studied eventually showed 90 per cent inhibition or more. An ulcer developed in the irradiated pouch of one animal. Simon's study indicates that the beta particles of P^{32} offer a new and potentially useful means of altering the activity of the cells of the gastric mucosa.

PHARMACOLOGIC GASTRIC SECRETORY INHIBITION

There are comparatively few papers in the literature which deal specifically with the effects of pharmacologic agents on gastric secretion. A tremendous number of tests of drug action, however, have been made. These, for the most part, have been secondary to the study of some other aspect of the secretory mechanism. Many papers containing such data have been missed. These omissions coupled with those made from ignorance make the presentation which follows a survey rather than a review.

One of the reasons for the shortage of specific pharmacologic data is lack of knowledge of the intimate details of the secretory process in the cells of the mucosa. This prevents the pharmacologist and his colleagues in the field of chemistry from selecting and then attacking a potentially vulnerable site in the chain of chemical reactions leading to the production of juice. To this restraining factor may be added the confusing array of preparations on which the action of drugs may be tested. For example, there are pouches of the entire stomach or portions of it in varying degrees of myenteric separation from the parent organ and with nerve supply intact or in different stages of central separation and peripheral degeneration. Each, therefore, presents a different possibility of altered pharmacologic sensitivity. These factors, too, make summarization of existing data difficult and generalizations from them distinctly tentative.

Cholinergic Blocking Agents. Atropine. Careful study of the action of atropine on gastric secretion commenced nearly seventy years ago and continues currently. The results of some of the investigations which have been made may be summarized as follows.

1. Basal, Continuous Fasting or Interdigestive Secretion. When loosely used these terms are synonymous. In most experiments the juice they designate is that collected after an overnight fast. Atropine greatly diminishes or abolishes this secretion in normal human beings (53, 147, 175, 220), in some patients with duodenal ulcer (161, 297) and in rats with duodenal ligation (286). When abnormal amounts of basal secretion are produced by transplanted gastric pouches in dogs (181) or by Pavlov pouches in Mann-Williamson dogs (155), atropine does not produce its usual decisive effect. The secretion of acid may be reduced

somewhat but it is not abolished (155, 181). The divergence from normal has been sufficient to prompt the suggestion that under these circumstances an abnormal mechanism may be operating.

2. Response to Meal. It has been known for many years that in dogs atropine reduces the secretory response of a Pavlov pouch to the ingestion of a meal (256). The result has been confirmed repeatedly (11, 173, 181). The output of acid is often reduced by 60 to 70 per cent and sometimes it is abolished. When the effect of atropine on the secretory response of the intact stomach to a meal is tested, as it is often in studies on human beings, complications arise, for the drug not only affects secretion but it also reduces motility. When the drug is given, the contents of the stomach may be greater and the acidity higher at various times during the course of the response to the meal, even though the output of acid by the mucosa may have been less. This plus the mixing of food with the juice and the lack of quantitative estimates of how much material passed from stomach to duodenum makes interpretations of studies on human beings in which ordinary test meals are used exceedingly difficult. As a consequence divergent results have been reported. Atropine has been found to increase (66), to inhibit moderately (206, 256, 265), or to have no effect on the secretory response of human beings to the ingestion of food. (For review, see articles cited and Altshuler [4] and Atkinson and Ivy [11].)

3. Cephalic Secretion. Workers in Pavlov's laboratory demonstrated before the turn of the century that atropine abolishes the gastric secretory response of dogs to sham feeding and to electric stimulation of the vagi (303). In dogs cephalic secretion induced by insulin is also abolished by atropine (191). In the cat atropine eliminates the secretion induced by hypoglycemic central stimulation (299) and that which follows electrical stimulation of the vagus nerve trunks or injections of eserine (306).

4. Gastric Phase. If food is placed directly in the stomach of a dog and at the same time any psychic stimulation is avoided the gastric phase of the secretory response to a meal will be induced. Sanozki (275) showed that atropine inhibited this type of secretion. Atropine will also suppress the response if the food is placed in an antral pouch of the stomach (330, 331). A Heidenhain pouch, because it is separated from the main stomach, has little or no vagal nerve supply, and the first portion of its response to the ingestion of a meal presumably is largely due to influences of secretagogues liberated in the stomach during the gastric phase and brought to the pouch by the blood stream. If enough atropine is given before a meal is eaten the response of the Heidenhain pouch is abolished; if it is given after secretion has commenced the output of acid is reduced but not completely suppressed (181). In transplanted gastric pouches which are completely denervated the response to the ingestion of a meal is also inhibited by atropine (181). Three stimulating factors, however, are involved in the secretory response of the stomach to the presence of the meal: (1) mechanical or physical contact between meal and mucosa, (2) secretagogues liberated from the food, and (3) secretagogues liberated by the mucosa (153, 154). The use of dogs with

Heidenhain pouches in tests of the effect of atropine on the gastric response to feeding does not separate the three factors.

5. Mechanical Stimulation. Lim, Ivy and McCarthy (201) have shown that atropine abolishes the secretory response of the mucosa to mechanical stimulation.

6. Secretagogues in Food. It has been known for years that extracts of meat will stimulate gastric secretion if they are given subcutaneously or intravenously (227, 331). All such crude extracts must contain histamine since it is a normal constituent of muscle, liver and lung. Kim and Ivy have been the only investigators to employ extracts free of this constituent (174). The action of their vasodepressor-free extracts, containing little or no histamine or histamine-like substances, was completely suppressed by atropine. The secretory action of those containing vasodepressor activity, owing no doubt to the presence of histamine or similar substances, was not so affected. The action of the secretagogue in extracts of meat therefore is most probably due to histamine or histamine-like compounds whose effects are resistant to atropine and another group whose action is seriously impaired by atropine. The latter group of substances may act directly on the cells of the mucosa or may act by liberating a secretagogue from the mucosa itself. Such a secretagogue might be gastrin or histamine.

"Gastrin" is the name given by Edkins to the secretagogue or secretagogues in extracts he made of pyloric mucosa (91). The original extracts undoubtedly contained histamine and this is also true of many of those used in later studies. Whether gastrin and histamine are the same or different substances is still controversial, although recent evidence substantiates the claim for their separate identity. (For a review of present status of subject, see Grossman [126].) Tests of the effect of atropine on the secretion evoked by the extracts has not aided their separation. Atropine has consistently failed to abolish the acid secretory response to crude extracts (91), partially purified extracts (173), or highly purified extracts (183). At best it only partially inhibits the secretion evoked by the extracts. Yet atropine can completely suppress the response to a meal. Thus, if gastrin participates in the response to a meal, atropine must inhibit prandial secretion by preventing the liberation of gastrin (112, 154, 181). By the same reasoning, if histamine participates in the secretory response to a meal, atropine must also prevent its liberation.

7. Intestinal Phase. When a dog with an esophageal-duodenal anastomosis and a pouch of the entire stomach is fed by mouth, secretion from the pouch represents pure intestinal phase juice. This secretion is completely abolished by adequate doses of atropine (112, 159). Again, if histamine is the humoral agent responsible for the secretion of the pouch, atropine must act by preventing its liberation.

8. Histamine. In general, atropine is not an effective inhibitor of gastric secretion induced by histamine. A relationship does exist between the size of the dose and the result, however, for larger amounts of atropine produce greater reductions of secretion with smaller doses of histamine, but atropine never seems

to erase the effects of histamine. This is particularly so in human beings. The output of acid apparently may be reduced, but the changes are small (245). Sometimes none is noted (202). Toxic effects may be present before significant inhibition occurs (11). The volume of the juice secreted by patients with duodenal ulcer may be reduced without the pH being affected (176). (For a discussion of reasons for inconsistencies in the observations on human beings, see Gray [112].)

In dogs, accumulated evidence clearly indicates that atropine does have an effect on gastric secretion stimulated by histamine. For example, the secretory response of Pavlov pouches to histamine is always reduced by atropine, the degree of inhibition ranging from insignificant to as high as 72 per cent depending upon the doses used (11, 155, 173, 200). In pouches of the entire stomach, atropine is about as effective in diminishing the response to histamine when the vagi are intact as when they are sectioned (236). Gray has made a most accurate study on the effect of varying doses of atropine in dogs with vagotomized pouches of the entire stomach (112). When the output of hydrochloric acid of the pouches was held at 5 mg. per minute by repeated injections of histamine, 0.5 mg. atropine produced 24 per cent inhibition, 1.0 mg. 37 per cent and 2.0 mg. 43 per cent. In our laboratory atropine has been found to reduce the output of hydrochloric acid of Heidenhain pouches, secreting continuously in response to histamine, by about 25 per cent (unpublished data).

The mechanism involved in the inhibiting effect of atropine on secretion induced by histamine poses two interesting questions: (1) Is some portion of the secretory response to histamine of nervous origin? (2) Is atropine, by acting directly on the secretory cells, capable of blocking some of the stimulating effects of histamine?

9. Alcohol. Doses of atropine in the customary therapeutic range will reduce but not abolish the secretory response to alcohol (113, 172). Large doses, however, may abolish the response (189, 237).

10. Thermal Trauma. Necheles, Prescott and Olson (232) have found that atropine does not affect the increased gastric secretion which follows burns.

11. Topical Application. Atropine applied directly to the mucosa may reduce its response to contact with food (83) without affecting its response to subcutaneous injections of histamine (202).

Substitutes for Atropine. In a study in which the effects of atropine, bellafoline, novatropine and methatropine in patients with duodenal ulcer were compared, Atkinson and Ivy (11) found that atropine was as effective as any of these substances in reducing the volume of juice and the output of hydrochloric acid secreted in response to histamine. In order to cause a depression of secretion, all drugs had to be given in amounts sufficient to produce dryness of the mouth, blurring of vision or fullness in the head.

Methylscopolamine has been found to be somewhat more effective than atropine in reducing the gastric secretory response of dogs to hypoglycemia (299). Popielski noticed many years ago that scopolamine hydrochloride had little or no effect on gastric secretion induced by the subcutaneous injection of histamine (248).

Dibutyl urethane of dimethyl ethyl-β-hydroxyethyl ammonium sulfate (dibutoline or dibuline) has been found to reduce the secretory response of pouches of the entire stomach to injections of histamine and to produce a prompt but transitory suppression of the basal secretion in patients with duodenal ulcer (220). Further tests have indicated that the action of the drug on the interdigestive secretion of patients with duodenal ulcer is variable, transitory and unpredictable (195).

Quaternary Ammonium Salts. The intravenous injection of 400 to 600 mg. of tetra-ethyl-ammonium chloride has been found to reduce basal secretion of human beings by about 88 per cent and the secretory response to a continuous infusion of histamine by about 70 per cent (336). Ethyl dimethyl beta (9-xanthene carboxylate) ethyl ammonium chloride (banthine) is the first derivative of this family of compounds to have practical therapeutic possibilities for the control of gastric secretion of patients with ulcer (210). Oral and intravenous administrations of the drug result in a pronounced reduction in the continuous gastric secretion of human beings. The margin of safety between inhibitory effects and toxic manifestations seems sufficiently large to justify more thorough laboratory and clinical trial.

Hexamethonium Iodide (C6). Kay and Smith have investigated the action of this compound on gastric secretion (170). The spontaneous morning and night secretions of patients with duodenal ulcer were reduced by the intramuscular injection of 100 mg. of this drug and a similar dose inhibited the secretion induced by hypoglycemia. Secretion provoked by histamine was unaffected. Prolonged inhibition of gastric motor activity followed its administration. The pain of ulcer and hunger were relieved. Some mild side effects occurred. Further testing with this compound will be necessary before its clinical usefulness can be assessed, but the results of this preliminary investigation certainly justify its further study.

Parasympathomimetic Drugs. Gray and Ivy (114) have shown that subcutaneous injections of acetyl-β-methylcholine chloride (methacholine chloride) every ten minutes in dogs produces a pronounced stimulation of gastric secretion which reaches a peak in about one to two hours and thereafter declines, often to extremely low levels. The decline can be hastened by giving larger doses from the outset or by administration of a large dose at the peak of the response (114, 295). Similar results have been obtained with acetylcholine (114). The effect may be described as "auto-inhibition". If the parasympathomimetic drugs are given in stimulating doses during a secretory response to histamine or if histamine is given while they are stimulating secretion, an augmentation of secretion is observed (114, 233, 262, 295). If, on the other hand, histamine is given during the period of auto-inhibition produced by the parasympathomimetic drug, its effects are greatly reduced (114). Likewise, large doses of methacholine chloride will inhibit the continuous secretion of gastric juice produced by repeated injections of histamine (114). Atropine abolishes both the excitatory and the inhibitory actions of methacholine (114).

The means by which the auto-inhibitory state is produced is not known. Does it mean that there are inhibitory influences which may be excited through the peripheral cholinergic mechanism? In anesthetized cats, acetylcholine has not been found to produce secretion of hydrochloric acid but only a scanty flow of mucus (306). Injection of the compound into the arteries supplying the stomachs of dogs often will produce mucous secretion and little or no acid (296, 313). The effect is similar to that produced by weak electrical stimulation of the vagus nerves, which has been observed to stimulate mucous secretion (23, 312). There is again the interesting possibility of the simultaneous occurrence of mucous secretion with acid inhibition. An inhibitory state may also occur in the mucosa after injections of histamine. Alley (1) found that in dogs the response to sham feeding was reduced when such feeding was carried out immediately after cessation of secretion provoked by histamine. Tests have not been made to determine whether other forms of secretion induced by nervous mechanisms are affected by a previous response of the mucosa to histamine.

Comment. Complete atropinization is sometimes considered the equivalent of vagotomy. More, however, is accomplished than when the nerves are sectioned. After vagotomy, peripheral cholinergic nervous elements remain in the wall of the stomach and atropine can block whatever effects they are capable of producing. Also, it is possible that atropine, particularly in large doses, may directly depress the secretory activity of the mucosal cells. The decisive and well-established action of atropine is, however, to block cholinergic influences at the mucosal cells, so that impulses reaching the peripheral cholinergic system via parasympathetic nerve trunks and any which may arise locally in the wall of the stomach are prevented from having their effect on the secretory cells.

Sympathomimetic Drugs. Epinephrine. The overwhelming impression derived from a review of literature dealing with the effect of epinephrine on gastric secretion is that it does not have an important action on the secretory process. In some tests it increased gastric secretion, in others it decreased secretion and in still others it had no effect (references to work on human beings: 140, 207, 226, 265, 279, 300, 329; dogs: 145, 158, 263, 288; cats: 23, 24, 199). Most changes reported have been small. A systematic search has not been made of its effect on the excitability of the mucosa to other stimuli but such changes as have been observed when it has been given with other stimuli have been small and variable.

Adrenergic Blocking Agents. Ergotamine. As might be expected from the results obtained with epinephrine, ergotamine has not been found to have much effect on gastric secretion. Most of the tests have been carried out on human beings (11, 62, 144, 166). The drug has been given subcutaneously (11, 62, 144) and intravenously (166) and its effects tested on secretion induced by test meals (11, 62, 144) or by injections of histamine (11). The results have been conflicting. At times the experiments have been complicated by the patient's nausea, and this plus the inaccuracies inherent in fractional gastric analysis of human beings leaves doubt as to whether ergotamine has any action on the types of secretion tested in these experiments. In experiments in animals it has been found to reduce the secretion of mucus produced in the stomach by the stimulation of partially degenerated splanchnic nerves (23). On theoretical grounds ergotamine would not be expected to have much effect on the normal secretory process in which a minor role has certainly been assigned to the sympathetic nerves. Under conditions in which the effects of sympathetic nerves were prominent or unopposed in the stomach this family of drugs might have some action.

Mucosal Anesthesia. Zeljony and Savich (330) demonstrated that the secretion produced in the stomach by mechanical or chemical stimulation of a pouch of the antral region is abolished by anesthetization of the pyloric mucosa with a solution of cocaine. Others have tested the effect of solutions of procaine hydrochloride on mechanical stimulation of gastric secretion (201). Gregory and Ivy (123) have expanded the findings, with the use of mucosal anesthesia as a means of elucidating the mechanism of local mechanical and chemical stimulation of gastric secretion. They used dogs with transplanted fundic pouches and pouches of the remaining main portion of the stomach. Anesthetization of the main pouch by perfusion with procaine solutions suppressed completely its secretory response to mechanical stimulation and to chemical stimulation by secretagogues of liver. If the secretagogues were placed in the unanesthetized stomach or intestine, the anesthetized transplanted pouch responded by secreting gastric juice. It seems most probable that the secretagogues of liver act by liberating an agent in the mucosa which may stimulate secretion locally and certainly can stimulate secretion when carried via the blood to other portions of gastric mucosa. Anesthetization of the mucosa abolishes its release.

Uvnäs (304) has found that in cats a secretagogue is liberated from the pyloric region into the blood during electrical stimulation of the vagus nerves and that its liberation is prevented by local cocainization of the pyloric mucosa.

It may be concluded that local anesthetization of the gastric mucosa by cocaine or procaine hydrochloride prevents the mucosa from liberating its secretagogue or secretagogues during mechanical, chemical (meat secretagogues) or nervous stimulation. The drugs are therefore important and effective inhibitors of a specific step in the secretory process.

Antihistaminic Agents. Considerable evidence has accumulated indicating that histamine participates normally in the mechanism of stimulation of gastric secretion. (For review, see 126.) Agents which destroy histamine or block its action offer, therefore, a potential means of inhibiting gastric secretion.

Enzymic Agents. Diamine Oxidase (Histaminase). In 1929 and 1930 Best and McHenry (29, 30) demonstrated the presence of an enzyme in various tissues which inactivates histamine. Zeller and associates have extended their findings and have shown that the enzyme deaminates a whole series of diamines by oxidation and have hence suggested the name "diamine oxidase" (92, 332, 333, 335). Soon after the enzyme was discovered its effect on gastric secretion was tested. The original preparations reacted slowly with histamine so that destruction of significant amounts of histamine often required some hours (30). The parenteral administration of these products was found to be without effect on secretion stimulated by injections of histamine (10, 13, 230) or the ingestion of a meal of meat (230). Some preparations of diamine oxidase have produced toxic symptoms when injected intravenously into dogs, and these inhibited gastric secretion even when the enzyme had been inactivated (264). Recently, purified preparations have shown inhibitory action when assessed against secretion induced by feeding or by injections of histamine, methacholine chloride or the urethane of beta-methylcholine chloride (urecholine) (127). No general toxic symptoms were produced by their injection although some of the preparations contained a potent vasopressor substance. It is not known whether or not the inhibition of gastric secretion produced by these preparations was due to diamine oxidase or some other constituent.

It should be emphasized that from a physiologic point of view none of these preparations would be expected to be effective if given by mouth. Best and McHenry (32) and Zeller and Schär (333, 334) have pointed out on a number of occasions that if the enzyme is taken by mouth it would be destroyed by the acid pH of normal gastric juice and that, if it escaped the acidity of the gastric contents, its emzymic properties would be abolished promptly by both pepsin and trypsin. Some of the enzyme might escape these digestive factors but under ordinary circumstances this would be a small proportion indeed of the total ingested.

Histamine Blocking Agents (Synthetic Antihistaminics). Soon after the antihistaminic action of some of the Fourneau series of compounds had been discovered by Bovet and Staub (41), Loew and Chickering (209) demonstrated that Fourneau 929 did not inhibit gastric secretion induced in dogs by the injection of histamine. The observation was soon extended to Fourneau 1571, the other active member of this series, and to tests with other types of secretory stimulants (40, 52, 130). In the main the compounds did not show specific antihistaminic effects on gastric secretion. Results with more recent members have been just as disappointing (105, 133, 150, 171, 274, 281). In fact in some instances the presence of the antihistaminic agent has resulted in an increase in secretion (209, 326). When reduction of secretion has occurred (130, 193, 214–216), it may possibly have resulted from the feeble atropine-like action known to be associated with many antihistaminic compounds (208). It may be concluded that the synthetic antihistaminic compounds so far tested do not block the action of histamine on the cells of the gastric mucosa. Study of the pharmacologic problem involved presents interesting possibilities for advancement of knowledge regarding the action of histamine. What is the nature of the difference between histamine's combination with a smooth muscle cell and a parietal cell?

Posterior Pituitary Extracts. It was first reported, on the basis of rather sketchy tests, that the subcutaneous injection of posterior pituitary preparations reduced the gastric secretion of patients with various disorders (56, 90, 107). Dodds and his co-workers have made a detailed study of the effects of large doses of posterior pituitary preparations on gastric mucosa and gastric secretion in animals. They have found that a single large subcutaneous injection of posterior pituitary extract produces temporary collapse, bloody diarrhea and loss of appetite in rabbits. If the animals are examined in the early stages of the reaction, acute gastritis, confined to the acid-secreting area of the mucosa, is found (85, 87). Repeated oral or subcutaneous administration of the extracts was found to lead to production of single punched-out ulcers in the acid-bearing area of the stomach (86) which could be prevented by the continuous administration of sodium bicarbonate (84). The gastrotoxic factor was found to be associated with the pressor and not the oxytoxic fractions of the extracts (85). When the effects of the extracts on gastric secretion were tested, pronounced inhibition was observed (71). The tests were made in anesthetized rabbits and cats secreting in response to histamine and in unanesthetized cats stimulated by injections of pilocarpine or insulin or by sham feeding. Pancreatic secretion was affected almost as dramatically as gastric secretion.

In an earlier study on dogs, Atkinson and Ivy (12) did not observe changes in the gastric secretory response of two dogs with Pavlov pouches to a meal by daily subcutaneous injections of 1 cc. of pituitrin or pitressin. Much larger doses have been used by Dodds and his co-workers to produce acute lesions in rabbits (87). Gray, Harris and Wieczorowski (116) have confirmed the finding that intravenous injection of posterior pituitary extract inhibits gastric secretion. They used a double histamine test in dogs with pouches of the entire stomach and found that 4 units of pituitrin produced about as much inhibition as 3 mg. of urogastrone (50 to 60 per cent).

The mechanism of the inhibition has not been determined although experiments by Dodds and his co-workers indicate that it may be related to reduced flow of blood through the stomach produced by the extracts (72). Further study of the secretory inhibition produced by posterior pituitary extracts is needed.

Antimalarial Drugs. Quinine and Quinacrine. Babkin and Karp (20) have found that 0.2 to 0.3 gm. of quinine or 0.05 to 0.1 gm. of quinacrine given intravenously to dogs weighing 8 to 15 kg. inhibits the secretion of gastric juice induced by electrical stimulation of the vagi, while secretion in response to histamine is unaffected. The doses of the drugs used were large and presumably had to be to produce their effect on secretion.

Biguanide Compounds. Burn and Vane (54) have tested the effect of paludrine (N_1-p-chlorophenyl-N_5-isopropyl-biguanide acetate) and a related series of compounds on gastric secretion induced by injections of histamine in anesthetized cats. Paludrine and a similar compound, in which the isopropyl group of paludrine is replaced by a methyl group, were found to have definite inhibitory action on gastric secretion. Subsequent study on human beings has shown that 0.9 to 1.0 gm. of paludrine by mouth will reduce significantly the concentration of acid in juice secreted in response to a test meal of gruel (88, 309). When given intravenously the drug has had no effect on secretion induced by histamine (88). Further work will be necessary to determine the mode of action of paludrine and other antimalarial drugs. The preliminary results indicate that these drugs may be useful in controlling certain types of secretion.

Antienzymic Agents. Urease Inhibitors. Urease is present in gastric mucosa

(212, 213) and in gastric juice (221). The activity of urease in the gastric mucosa of human beings is roughly proportional to its ability to secrete acid (109), and in dogs and human beings its maximum concentration occurs in the region of the parietal cells (109, 203). Mann and Mann (218) have made a systematic study of the effect of inhibitors of urease on gastric secretion provoked by histamine in dogs (218). Solutions of the inhibitors were applied directly to the mucosa, allowed to remain there for a few minutes only and then histamine was given. The heavy metals known to inhibit the enzyme reduced the secretion of acid; those which did not have an effect on the enzyme likewise did not have an effect on secretion. Hydrogen peroxide, quinone, brilliant green and crystal violet, all of which inhibit the enzyme, also lowered the acidity of the juice. The result with hydrogen peroxide confirms earlier observations of Culmer, Atkinson and Ivy (67) who found that lavage of gastric mucosa with 0.5 to 3 per cent solutions of hydrogen peroxide in dogs consistently reduced the acidity of the juice secreted in response to histamine. Less consistent inhibition was obtained when gastric secretion was induced by feeding. The results for human beings also were variable. The secretion of mucus was usually greatly increased and irritation of the mucosa with the strong solutions may have played a part in the inhibition. Mann and Mann, however, used weaker solutions and observed some inhibition. They have pointed out that although their results may be explained on the basis of a temporary inactivation of urease, other enzymes in the gastric mucosa may have been affected.

Carbonic Anhydrase Inhibitors. The enzyme, carbonic anhydrase, has been demonstrated in the gastric mucosa of rats, cats and dogs (73, 74, 78). The possible role of this enzyme in the production of gastric juice has been discussed recently by Davenport (77). He has demonstrated that the oral administration of sodium thiocyanate to dogs results in a diminution in the rate of secretion and the concentration of acid in juice secreted in response to histamine (75). Intravenous injection of thiocyanate has been found to produce even more pronounced inhibition of gastric secretion in anesthetized dogs (255). Sulfanilamide, which is another inhibitor of carbonic anhydrase, has also been tested and has been found to reduce gastric secretion in dogs (76).

Whether or not the substances tested in these studies produced their effects by inhibiting the enzyme against which they were theoretically directed is not settled. In the end it may be unimportant, for through them a new and provocative approach to the investigation of gastric secretory inhibition has been opened.

CONCLUSIONS

An entirely satisfactory inhibitor of gastric secretion is not available today. However, a number of promising possibilities are being studied by different workers and new avenues of approach to this old problem have been opened recently. If opportunity to challenge these potentialities continues uninterrupted, a specific inhibitor suitable for investigative and therapeutic use should be found.

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